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# DEFICIENCY ANEMIA IN INFANTS

## REPORT OF TWO CASES, WITH ASSOCIATED TEMPORARY DEFICIENCY OF ANTI-ANEMIC FACTOR IN ONE AND ALLERGY AND ABNORMAL DIGESTION OF PROTEIN IN THE OTHER

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In this communication I wish to report 2 unusual cases of nutritional anemia in young infants and to discuss the problems of therapy to which they gave rise. It should be emphasized that nutritional anemia is a comprehensive term referring to a group of conditions dependent on poor nutrition of the hemopoietic system. Pediatricians in the past have regarded nutritional anemia as synonymous with microcytic anemia due to lack of iron and have therefore considered it as due to faulty nutrition of the child in the sense of a deficiency of iron in the food. The pathologic physiology of nutritional anemia has been made clearer by studies such as those of Minot, Castle and Whipple. Moore [1] has tersely stated the facts as follows: "The term nutritional anemia should no longer be used to denote the hypochromic anemia of infancy and childhood. Our knowledge of the relationship of essential nutritional factors to formation of red cells and synthesis of hemoglobin has progressed to the point at which it is recognized that deficiencies of numerous nutritional substances may result in the production of an anemia."

Castle and Minot [2] classified the anemias into two main groups: (*A*) anemias mainly due to loss or increased destruction of blood (bone marrow physiologically hyperactive), and (*B*) anemias mainly due to decreased blood production (bone marrow physiologically hypoactive). Under the second heading, as one of five subdivisions, they put "nutritional anemia of the blood-forming organs." This type of anemia may appear as (*a*) macrocytic anemia due to deficiency of certain intrinsic factors, pernicious anemia; (*b*) hypochromic anemia due to deficiency of iron and other substances concerned especially with production of hemoglobin; (*c*) anemia due to deficiency of vitamin C, or (*d*) anemia due to deficiency of thyroid secretion.

It is subgroup *b*, hypochromic anemia due to deficiency of iron and other substances concerned especially with production of hemoglobin, that is of special interest in this communication. In the majority of instances, severe anemia in early infancy is due to deficiency of iron; but, as Castle and Minot have stated in their classification, hypochromic anemia may also be due to deficiencies of other substances concerned with production of hemoglobin, and it is important in the treatment of hypochromic anemia that one keep these other substances in mind. There are reports in the literature of numerous instances of nutritional anemia in infants refractory to exhibition of iron alone but yielding rapidly to injection of liver. In some of these reports the anemia has been described as macrocytic, that is, allied to pernicious anemia of adults; in others, however, the conditions described do not seem to differ hematologically from hypochromic anemia due to a deficiency in iron. The first of these two types is exemplified by the condition in a patient described by Bachman,[3] an infant whose blood contained 3,200,000 to 3,480,000 red cells per cubic millimeter and had a hemoglobin content of 74 to 83 per cent. The color index was at times as high as 1.26. When this infant was fed liver extract daily the blood picture changed rapidly: The number of red cells per cubic millimeter increased to 5,000,000; the hemoglobin content rose to 92 per cent; the color index approached unity, and the proportion of reticulocytes rose from 3.4 per cent to 8.4 per cent. During this short period of recovery the general nutrition of the baby improved and he gained weight rapidly. Anemia in which the blood picture is predominantly microcytic but in which liver is essential in the therapy is exemplified by the condition described in the report of a

From the Pediatric Service of the Mount Sinai Hospital.

1. Moore, C. V.: Ohio State M. J. **35**:25, 1939.

2. Castle, W. B., and Minot, G. R.: Pathological Physiology and Clinical Description of the Anemias, New York, Oxford University Press, 1936.

3. Bachman, A. L.: Macrocytic Hyperchromic Anemia in Early Infancy: Report of Case and Review of Literature, Am. J. Dis. Child. **52**:633 (Sept.) 1936.

case recently published by Fouts and Garber.[4] This report concerns a 4 month old infant whose mother had been on a meat-free diet during pregnancy. At 2 months of age the infant seemed healthy, though it weighed only 8½ pounds (4,500 Gm.). After the infant had had an infection of the upper respiratory tract accompanied by vomiting, severe anemia developed, with the number of red cells as low as 910,000 per cubic millimeter of blood. In spite of large doses of iron and vitamins and transfusions totaling 478 cc. of blood, there was no improvement. After futile treatment had been given for several months, daily injections of liver produced a dramatic increase in the number of reticulocytes, the total number of red cells and the amount of hemoglobin and rapidly cured the condition.

TABLE 1.—*Laboratory Data for Mary T. (Case 1)*

| Date | Hemoglobin, % | Red Blood Cells per Cu. Mm. | Platelets per Cu. Mm. | White Blood Cells per Cu. Mm. | Polymorphonuclear Neutrophils, % | Lymphocytes, % | Basophils, % | Eosinophils, % |
|---|---|---|---|---|---|---|---|---|
| 11/20/42 | 17 | 929,000 | 80,000 | | | | | |
| 11/21 | 54 | 2,600,000 | ..... | ..... | 10 | 86 | 2 | 2 |
| 11/24 | 56 | 2,340,000 | | | | | | |
| 11/25 | 45 | 2,340,000 | | | | | | |
| 11/28 | 37 | | | | | | | |
| 11/30 | 45 | 2,380,000 | | | | | | |
| 12/ 3 | 37 | 1,950,000 | ..... | 7,150 | 32 | 66 | 2 | |
| 12/ 7 | 43 | 2,050,000 | | | | | | |
| 12/20* | 38 | 1,960,000 | ..... | 5,600 | 29 | 64 | 5 | 2 |
| 12/23 | 44 | 2,540,000 | | | | | | |
| 12/24 | 45 | 2,610,000 | | | | | | |
| 12/28 | 60 | 3,180,000 | | | | | | |
| 1/ 5/43 | 71 | 3,870,000 | | | | | | |
| 1/ 9 | 80 | | | | | | | |
| 1/13 | 76 | 4,000,000 | | | | | | |
| 1/22 | 72 | 3,930,000 | | | | | | |
| 1/27 | 77 | 3,920,000 | | | | | | |
| 1/29 | 84 | 4,350,000 | | | | | | |
| 2/ 3 | 81 | 4,100,000 | | | | | | |

* On December 16 injections of liver extract were started.

The following brief report concerns a similar condition in a patient recently admitted to Mount Sinai Hospital.

CASE 1.—Mary T. was admitted to the pediatric service of the Mount Sinai Hospital on Nov. 29, 1942, at the age of 6 months, with the complaint of weakness and pallor. The mother, aged 23, and the father, aged 30, were well, and there was no familial history of tuberculosis, cardiac disease or anemia.

The child had been born May 2, prematurely, at 7 months. Delivery was spontaneous, after a short labor. There was no cyanosis or jaundice. The weight at birth was 5 pounds 4 ounces (2,400 Gm.). The infant was fed a preparation of dried milk (S. M. A.), the amount of which had been gradually increased, and at the time of admission to the hospital she was taking 55 Gm. in 670 cc. of water daily. Beginning at the age of 3½ months, she received 3 to 5 drops (0.18 to 0.3 cc.) of a medicine containing iron daily for four weeks; administration of this medicine was stopped at the onset of a cold. The mother says the child took the medicine well and did not regurgitate it. At the age of 5 months the child started taking cereal, 2 tablespoons (30 cc.) of oatmeal in the morning and 1 tablespoon (15 cc.) at night. Since she was 4 months old, she had been taking vegetables daily, 1 to 1½ tablespoons (15 to 22 cc.) of green beans, beets, carrots or peas. The cereals and vegetables were taken well and were never vomited. Orange juice, 2 ounces (60 cc.) twice daily, was taken from the second to the fifth month; none was taken during the month preceding hospitalization. Vitamins A and D were supplied in an "oily" solution, 1 teaspoon (5 cc.) daily.

Three weeks before admission to the hospital the infant had a running nose, a slight cough and a temperature of 100 F. for about a week. The child had always had good color, with rosy pink cheeks; but, with the onset of the cold, the parents noticed that she was becoming pale. Though the pallor became progressively worse, no medication was given. During the last two weeks before she entered the hospital, the infant became more and more listless, lost her appetite, moved about less and less and finally became unable to hold up her head. No bleeding or ecchymosis was noted. There was no fever or vomiting, and the bowels were normal.

Physical examination revealed a well developed, fairly well nourished, lethargic infant weighing 11 pounds (5,000 Gm.). The child was extraordinarily pale. When she was first seen at the hospital, while asleep, the alabaster color of her skin led several people to think that she was dead. The skin was dry, but the turgor was good. There were no petechiae or ecchymoses on the skin or the mucous membranes. The head, skull, eyes, nose, mouth, pharynx and ears were normal. The gums were normal, and there were no teeth. The superficial lymph nodes were not enlarged. There was no costal beading. The lungs were normal. The heart appeared enlarged to the left; the cardiac rate was rapid (160), and over the entire precordium there was heard a loud, coarse systolic murmur. There was no cyanosis and no clubbing of the fingers or toes. The abdomen was soft; the edge of the liver was palpable 3 cm. below the costal margin; and the spleen could not be felt. There were no evidences of scurvy. The infant was unable to hold up her head.

The urine contained no albumin, sugar, bile or urobilinogen, and no formed elements were found in it. Tuberculin and Wassermann tests gave negative reactions. The hemoglobin content of the blood was 17 per cent and the red cell count 920,000, with evidence of severe polychromasia, poikilocytosis and anisocytosis and moderate basophilic stippling. There

4. Fouts, P. J., and Garber, E.: Nutritional Anemia in Infant Responding to Purified Liver Extract, Am. J. Dis. Child. **64**:270 (Aug.) 1942.

were 11,000 white cells per cubic millimeter of blood, of which 10 per cent were polymorphonuclear leukocytes, 85 per cent were lymphocytes, 2 per cent were basophilic leukocytes and 2 per cent were eosinophilic leukocytes. There were 80,000 platelets per cubic millimeter of blood. A culture of material from the throat showed pneumococcus type XIII. A diagnosis of extremely severe nutritional anemia or leukemia was considered when the child was admitted to the hospital, and a blood transfusion was given at once. Iron and large doses of vitamins were prescribed.

Roentgenograms of the skull and long bones were normal. Gastrointestinal roentgenograms showed no abnormalities. An electrocardiogram and phonocardiograms revealed an early systolic murmur but no other changes. Sternal puncture revealed bone marrow reported as containing a predominance of young erythroblastic cells, a condition which suggests a defect in maturation. A similar picture is seen in pernicious anemia.

In spite of repeated transfusions, the child's condition changed little (table 1); and beginning December 16 intramuscular injections of liver (Wilson's liver extract) were given, 0.25 cc. the first day, 0.5 cc. the second day and thereafter 1 cc. every other day. A total of 11 cc. was given. At this time the hemoglobin content of the blood was 38 per cent and the number of red cells per cubic millimeter was 1,900,000. Within one week the content of hemoglobin had risen to 60 per cent and the number of red cells to 3,180,000, and within two weeks the hemoglobin content was 80 per cent and the number of red cells, 4,000,000. The proportion of reticulocytes rose from 2 per cent to 16 per cent. The infant made an uninterrupted recovery, and she was discharged from the hospital February 4, weighing 12 pounds 15 ounces (5,850 Gm.). Reports several months later showed that the child was cured.

## COMMENT

Although there is no history of inadequate maternal diet during pregnancy, this case closely parallels the case reported by Fouts and Garber. It is interesting to note that in both cases the anemia appeared suddenly, after an apparently mild infection of the upper respiratory tract. It seems likely that some infants possess only enough hemoglobin-producing substances to carry them along until an infection destroys the balance; then a severe anemia results. That there is a definite relationship between anemia and infection is common knowledge. Whipple and his co-workers have continually emphasized the great susceptibility of anemic dogs to infection. Moreover, acute infections which are ordinarily not thought of as productive of anemia may cause considerable unsuspected lowering of the hemoglobin. The anemia often accompanying pneumonia in children exemplifies this relation.[5]

Exactly what factor in liver is responsible for the rapid recovery of infants with this type of anemia is not known. The vitamin B complex, especially vitamin $B_2$ (riboflavin), has been mentioned, and cases are on record in which anemia, both experimental and clinical,[6] has been improved by its use, though many hematologists are skeptical as to its value in this connection.

Though such iron-resistant anemia in infants is not common, it occurs occasionally and must be kept in mind. As I shall mention later, the condition of the alimentary tract may have much to do with the inability to absorb from food the substances necessary to build hemoglobin. This accounts in part for the anemia seen in conditions such as sprue.[7] However, anemia in infants not cured by blood transfusion or iron may yield to liver given by mouth.[8]

The second case to be reported is also one in which a severely anemic infant failed to improve with long-continued treatment with iron and frequent blood transfusions. In this case, however, cure was obtained without the use of liver or of parenteral medication.

CASE 2.—Theodore L. was admitted to the Mount Sinai Hospital on Feb. 10, 1943, at the age of 5 months, weighing 8 pounds 7 ounces (3,800 Gm.), with the complaint of vomiting, anemia, persistent eruption and failure to gain weight.

The family history was normal. The infant was the first child of young, healthy American parents. There was no familial history of hay fever, asthma or allergic eruptions. Birth which occurred Sept. 12, 1942, was spontaneous, at term, after a thirty-six hour labor. Pregnancy had been normal. The infant's weight at birth was 6 pounds 12 ounces (3,050 Gm.). Because of lack of breast milk, he was given a formula of water, evaporated milk and dextrimaltose. On the fourth day of life, while he was still in the hospital, an erythematous eruption appeared on the forehead. On the tenth day the child weighed 6 pounds 6 ounces (2,890 Gm.) and was taken home. The rash was then found to have spread over the entire body; it was red and weeping. For the next four days the formula of evaporated cow's milk was continued, the infant taking it poorly and gaining little. The rash became much worse, and it was thought to be allergic in origin. This conclusion was supported by the presence of eosinophilia; from 20 to 40 per cent of the leukocytes were eosinophilic. For this reason goat's milk was substituted for evaporated cow's milk in the formula. The eruption subsided immediately and has remained under fair control.

An attempt to change back to a diet of cow's milk, when the child was 2 months old because the infant refused to eat and consequently lost weight rapidly, resulted promptly in an exacerbation of the eruption. At that time (Nov. 12, 1942) the infant weighed only 7 pounds 2 ounces (3,250 Gm.). It was then that the family first noted that the baby was becoming much paler. The content of hemoglobin in the blood (November 29) was found to be only 36 per cent, and a

5. Bass, M. H.: The Association of Anemia and Pneumonia in Infants: Treatment by Blood Transfusion, Am. J. Dis. Child. **29**:318 (March) 1925.

6. (*a*) Buding, A.: Deutsche med. Wchnschr. **67**: 591, 1941. (*b*) Bomford, R. R., and Rhoads, C. P.: Quart. J. Med. **10**:175, 1941.

7. Castle, W. B., and Rhoads, C. P.: Observations on Etiology and Treatment of Sprue in Porto Rico, J. A. M. A. **99**:166 (July 9) 1932.

8. Rominger, E.; Meyer, H., and Bomskov, C.: Ztschr. f. d. exper. Med. **89**:786, 1933.

transfusion of 120 cc. of blood was given. The eruption then reappeared, but after a few weeks it cleared except in the folds in the skin of the groins and axillas. After the transfusion was given the child's appetite improved and, in spite of considerable vomiting, his weight rose to 9 pounds (4,080 Gm.).

About December 19 the child again began to refuse his feedings and to lose weight. Semisolid foods (cereal and puréed vegetables) were given without success. About this time general furunculosis appeared and vomiting became a more prominent symptom. A roentgen examination of the gastrointestinal tract revealed no abnormality. On January 16 a second blood transfusion was given. Three days later the hemoglobin content of the blood was 56 per cent, and the infant was again given a transfusion.

One week before admission banana was given to the infant, and it seemed to be tolerated fairly well. However, the infant vomited more frequently and appeared to be losing ground. A fourth transfusion, of 100 cc. of blood, was given, because the content of hemoglobin on February 5 had again dropped to 56 per cent. All attempts at feeding thereafter were unsuccessful, and the vomiting increased. The infant had a temperature of 101 to 103 F., and he became visibly dehydrated. His weight dropped several pounds.

From earliest infancy the child had received a multivitamin preparation and ascorbic acid. From the onset of the anemia good-sized doses of saccharated ferrous carbonate had been given. The infant's condition had became so much worse that hospitalization was urgently advised.[9]

Physical examination revealed a small, 5 month old infant, who was febrile, emaciated and dehydrated. The skin showed areas of eczematous thickening and

TABLE 2.—*Laboratory Data for Theodore L. (Case 2)*

| Date | Hemoglobin, % | Red Blood Cells per Cu. Mm. | Blood Transfusions, Cc. |
|---|---|---|---|
| 11/29/42 | 36 | 1,630,000 | 120 |
| 1/16/43 | .. | ..... | 110 |
| 1/19 | 56 | 2,530,000 | 100 |
| 2/ 5 | 56 | 2,700,000 | 100 |
| 2/11* | 87 | 4,450,000 | |
| 2/15 | 76 | 3,900,000 | |
| 2/18 | 74 | 3,860,000 | |
| 2/25 | 82 | 4,210,000 | |
| 3/ 2 | 75 | 3,980,000 | |
| 3/ 5 | 73 | 3,890,000 | |

* On February 10 the child was admitted to the hospital, greatly dehydrated.

reddening. The buttocks were excoriated, and remnants of furuncles were seen on the scalp. The eyes and ears were normal. There was a slight mucoid nasal discharge. The throat was intensely congested, and the tonsils were swollen. There was slight cervical adenopathy. The lungs were normal to percussion and auscultation, though fluoroscopy revealed shadows of some infiltration in the right mediastinal region. The heart was normal, and there were no murmurs. The abdomen was somewhat distended, and the liver was palpable 1 fingerbreadth below the costal margin. The spleen was not felt. A neurologic examination revealed no abnormality.

The urine was normal. The reactions to tuberculin and Wassermann tests were negative. The blood picture was as follows: hemoglobin, 87 per cent; red cells, 4,450,000; platelets, 150,000; white cells, 9,150; polymorphonuclear neutrophils 41 per cent; polymorphonuclear eosinophils, 3 per cent; lymphocytes, 51 per cent, and monocytes, 4 per cent.

The diagnosis made by the resident at the time the infant was admitted to the hospital was severe allergy, with malnutrition and anemia related to faulty intake and possibly due to defective metabolism, recent infection of the upper respiratory tract and, possibly, bronchopneumonia.

To relieve the dehydration, shown not only by the general appearance but by the high hemoglobin content and red cell count, an intravenous injection of 120 cc. of 10 per cent dextrose in an isotonic solution of sodium chloride was given. On account of the severe eczema, evidently allergic in origin, and the gastrointestinal symptoms, which were also thought to be due to allergy, a preparation containing the essential amino acids, Nutramigen, was prescribed for feeding. The composition of Nutramigen is as follows:

| | Per cent |
|---|---|
| Amigen [9a] | 20.0 |
| Dextrimaltose | 42.3 |
| Corn oil | 18.0 |
| Arrowroot starch | 10.0 |
| Powdered brewers' yeast | 3.0 |
| Calcium gluconate | 3.5 |
| Other mineral salts | 3.2 |

Vitamins were also continued daily as follows: ascorbic acid, 50 mg.; halibut liver oil with viosterol, 10 drops, and thiamine hydrochloride, 3 mg.

The day after admission to the hospital the child appeared remarkably improved. He took small amounts of the amino acid preparation well. The vomiting stopped at once with the new diet. He was febrile (temperature 101 F.) for only one day. Iron in the form of saccharated ferrous carbonate in the amount he had been receiving before admission (10 grains four times daily) was prescribed. The hemoglobin content and red cell count did not drop, as they had done previously, after the effect of the transfusions had worn off (table 1). The appearance of the bone marrow obtained by sternal puncture at the time the child was admitted was reported as follows: There was a serious decrease in the number of erythroblastic cells (about two thirds of the number usually seen at this age were found); otherwise the bone marrow was normal.

The feedings were gradually increased in amount; and, although the child did not gain weight, he looked and acted much improved. After about a week he began to gain. The skin cleared up completely, and the turgor became normal. Two weeks after he was admitted to the hospital, passive transfer tests were made for goat's milk, cow's milk, egg white, oats, rye, rice and wheat. The goat's milk and cow's milk produced questionable reactions, and the remainder of the results were negative.

The child was discharged on March 6, less than a month after admission, weighing 9 pounds 8 ounces (4,300 Gm.), a gain of over a pound. The skin had healed completely. Follow-up reports showed that the patient continued to do well and that three months after discharge from the hospital he was in excellent condition.

9. This patient was seen with Dr. David Goldberg, of Westwood, N. J., the infant's pediatrician. Dr. Goldberg provided the data of the history prior to hospitalization.

9a. Amigen is a preparation of hydrolyzed casein. Casein, containing, as it does, all known amino acids, is a "complete" protein, which is satisfactory for growth and maintenance. The casein is hydrolyzed by pork pancreas, and the resulting product contains all the essential amino acids.

COMMENT

In case 2 the condition reported may certainly be classed as nutritional anemia. In discussing it I wish to call attention to the following facts: The infant was allergic; he was fed goat's milk exclusively for several months; anemia developed which failed to respond to long-continued treatment with large doses of iron and vitamins and several transfusions and the condition was cured rapidly when the food used was changed to one in which the protein was in the form of amino acids.

The fact that the anemia occurred at a time when the infant was being fed goat's milk exclusively is of considerable interest, since the subject of anemia due to a diet of goat's milk is one which gave rise to a great deal of discussion a decade ago. There is no question that severe anemia develops in certain infants fed on goat's milk for a long period. Many European authors, moreover, claimed that this anemia differed from the ordinary anemia encountered when cow's milk was fed over a prolonged period in that it did not respond to the administration of iron. They believed that anemia due to a diet of goat's milk was a definite clinical entity, and there was much speculation as to its causation. A favorite theory was that the goat's milk contained certain fatty acids which destroyed the red cells of the blood and that the resulting disturbance was of a hemolytic type. This hypothesis was subsequently disproved, and the anemia was shown to be due to failure to produce hemoglobin, rather than to its destruction.

Rominger and his co-workers,[8] in 1933, questioned whether anemia due to a diet of cow's milk and that due to a diet of goat's milk were identical. They believed that, of the two, goat's milk anemia was a much more serious disease. They stated definitely that it was not due to a deficiency of iron and that iron used therapeutically was useless. The condition did yield to treatment with liver, and they therefore considered it akin to pernicious anemia and suggested that lack of some part of the vitamin B complex might be the underlying cause. They conducted a large series of experiments on infants and rats. They stated that by feeding rats a diet of cow's milk only they produced a chlorotic type of anemia curable by treatment with iron. When goat's milk was fed to 8 week old rats a similar result was obtained. However, when goat's milk was fed to rats 3 or 4 weeks old a different type of reaction followed and a hyperchromic type of anemia resulted. This type of anemia was not affected by the administration of vitamin C, but it was prevented by the addition of farina or of cream from cow's milk to the diet. Injections of liver extract acted both curatively and prophylactically. Rominger and his co-workers concluded that anemia which develops in a person on a diet of goat's milk is due to the lack of some exogenous factor which is furnished by liver.

In the following year György [10] also described anemia in infants fed goat's milk, but he was able to cure the condition not only with liver but with yeast. He was unable to duplicate Rominger's experiments on rats, for when he fed them goat's milk he obtained not a hyperchromic type of anemia but a chlorotic type similar to that resulting from the feeding of cow's milk. In a note appended to his article he suggests that the fact that Rominger used rats weighing 30 to 35 Gm. whereas his own rats were all larger might account for his failure to obtain like results.

Following these articles many papers on anemia due to a diet of goat's milk appeared in the literature and, in Germany especially, pediatricians reported cases in which the condition yielded to liver therapy.[11] The subject was in a confused state till work by American investigators threw new light on the problem. Kohler, Elvehjem and Hart [12] showed that anemia produced by feeding goat's milk to rats could be readily relieved by the exhibition of iron and copper. In other words, it was a condition similar to that produced by a diet of cow's milk exclusively, and liver or substances derived from liver were not necessary for its cure. However, these authors showed that, besides affecting the blood, the exclusive feeding of goat's milk resulted in poor development and slow growth of the experimental rats. When manganese was added to the food, growth was much more satisfactory. They found also that the nutritional state of the rats depended in part on the rations fed to the goats whose milk was being used. When the alfalfa fed to the goats was of a good grade the milk from the goats produced much better growth in the rats. "The growth of the rats fed goat's milk mineralized with iron, copper and manganese was much inferior to that obtained with cow's milk mineralized in the same manner. The deficiency in goat's milk for growth was not corrected by the addition of cod liver oil, yeast, liver or crystalline B. Normal growth was obtained by the addition of brain tissue." The authors were unable to explain adequately the difference between their results and those obtained by the German investigators, but they suggested that the composition of the goat's milk

10. György, P.: Ztschr. f. Kinderh. **56**:1, 1934.

11. (*a*) Mödlinger, P.: Kinderärztl. Praxis **9**:425, 1938. (*b*) Balde, J. H.: Arch. f. Kinderh. **117**:95, 1939.

12. Kohler, G. O.; Elvehjem, C. A., and Hart, E. B.: Am. J. Physiol. **113**:279, 1935.

may have been different or that the iron used in the treatment may not have been the same.

Other American investigators [13] obtained similar results, adding further evidence that "goat's milk itself was not deficient in any necessary organic hematogenic substance, such as the alleged 'extrinsic factor' related to pernicious anemia in man."

Apparently the discrepancies in the results obtained by different investigators may be explained by the fact that not all goat's milk is the same, that it varies depending on what the goats are fed and that there may be deficiencies in certain samples of milk not present in others, with a resulting difference in the effect on the animals fed the milk.

Another interesting question raised by the case of anemia due to goat's milk is: What part in the cure of anemia was played by the feeding of amino acids? Ever since the work of Abderhalden was published, the importance of the protein fraction of the hemoglobin molecule has been realized; and gradually more attention has been focused on it, especially in relation to the building of hemoglobin in the living body. It has been shown definitely that the addition of iron to a diet, without further change in regimen or diet, rapidly cures hypochromic anemia of infants. An example of the effectiveness of this therapy was reported by Denzer and me in 1925.[14] One of twins whose hemoglobin values were respectively 27 and 28 per cent was given iron, while the other twin was used as a control. The hemoglobin content of the blood of the treated infant rose in a few weeks to 70 per cent while that of the other twin, who received exactly the same diet with the exception of iron and was kept under identical conditions in the same ward, showed no change. In 1925 Hart, Steenbock, Elvehjem and Waddell [15] published work leading to the following conclusions: (1) Nutritional anemia develops in rabbits on a diet of milk; (2) inorganic iron alone added to the basic ration will not influence this condition; (3) inorganic iron in the presence of fresh cabbage, alcholic extract of desiccated cabbage or extract of corn meal will prevent or cure such an anemia (these extracts are free from iron), and (4) chlorophyll, free from iron, will also in the presence of added inorganic iron correct such an anemia. In other words, unless certain other factors are present in the diet, iron alone will not necessarily relieve anemia. This work helped to emphasize the importance of the protein moiety of the hemoglobin molecule.

In one of the Pasteur lectures given before the Institute of Medicine of Chicago,[16] G. H. Whipple stated that it is now well established that the production of hemoglobin in persons with anemia can be controlled by diet, iron and protein being the essential factors. Strict control of the intake of either iron or protein influences anemia in dogs. Whipple found that in this regard the most valuable foods were liver, kidney, stomach and pancreas. Muscle was not as potent as the visceral proteins. Prunes, apricots and peaches were especially potent, the value being found in their ash. Vegetables, dairy products, fish and many fruits were of little value. Iron is treasured by the body, and only traces escape. The globin is also saved and used over again to form new hemoglobin or to supply some other protein needed by the body.

Recently Saha and Guha [17] showed that in animal tissue 30 to 40 per cent of the total nonhemin iron consists of an iron-copper-nucleoprotein complex which can be obtained in a fairly pure state. If the iron and copper are split off and given in the same amounts without the nucleoprotein, the results in curing anemic rats are definitely poor. "This would indicate the importance of the organic moiety for hemoglobin building."

In recent years nutritional investigation has gone one step further; and not only the necessary proteins but their precursors, the amino acids, are being studied in this connection. Thus, for example, it has been shown that rats fed deaminized casein become anemic and die. Death can be prevented by the addition of casein to the diet. In experiments on the feeding of combinations of various amino acids it was shown that lysin particularly, when added to the diet, was instrumental in curing anemia.[18] The clinical use of work along these lines is only beginning, but it may prove to be of considerable value. Whipple and his co-workers have contributed great stores of information in this field and have pointed out that the results they have obtained may well be of use to clinicians. In a paper entitled "Hemoglobin and Plasma Protein: Simultaneous Production During Continued Bleeding as Influenced by Amino-Acids, Plasma, Hemoglobin and Digests of Serum Hemoglobin and Casein" Robscheit-Robbins, Miller and Whip-

13. Orten, J. M., and Smith, A. H.: Yale J. Biol. & Med. **8**:637, 1936.

14. Bass, M. H., and Denzer, B.: Iron Therapy in the Anemias of Infancy, J. A. M. A. **86**:938 (March 27) 1926.

15. Hart, E. B.; Steenbock, H.; Elvehjem, C. A., and Waddell, J.: J. Biol. Chem. **76**:67, 1925.

16. Whipple, G. H.: Proc. Inst. Med. Chicago **14**:2, 1942.

17. Saha, K. C., and Guha, B. C.: Nature, London **148**:595, 1941.

18. Hogan, A. G.; Powell, E. L., and Guerrant, R. E.: J. Biol. Chem. **137**:41, 1941.

ple[19] described in detail experiments on dogs which had been kept hypoproteinemic and anemic. In their introduction they said: "This paper shows that digests of serum, hemoglobin, and casein are well utilized to build new plasma protein and hemoglobin. More important perhaps is that the amino-acids necessary for growth supply the material out of which abundant plasma protein and hemoglobin can be produced. Some digests are improved by amino-acid supplements and cystine is an important amino-acid for this purpose. Amino-acids other than the 10 necessary for growth may be proved to accelerate plasma protein or hemoglobin building and therefore be valuable supplements to digests or to such amino-acid mixtures as promote growth." They pointed out that when these doubly depleted dogs were given injections of amino acids, plasma or hemoglobin or of digests of serum, hemoglobin or casein they invariably produced more hemoglobin than plasma protein. "Under all circumstances on all diets this was found to be true." "Further, the growth amino-acid mixture favors hemoglobin production more than any other materials tested —even hemoglobin itself or the digests." Their results showed that digests of casein were well used for this purpose and that they led to the formation of as much new plasma protein as any material tested. They say further "Amino-acid mixtures are of special interest. The growth mixture of 10 amino-acids (Rose) is well utilized by mouth or by vein and favors new hemoglobin production more than any material tested."

The dramatic improvement in the general condition of this infant was due only to the change in his diet. The home from which the child had come was a good one. The infant was an only child, and both parents were highly intelligent young Americans, so there was no question as to the general hygiene, nor was there any doubt that the physician's orders had been faithfully carried out. The complete change in the child's demeanor on his new diet was striking. He slept quietly; he stopped vomiting, and his eruption rapidly disappeared. Such results are seen often when the correct diet is prescribed for an allergic infant. What made this case unique in my experience was the change in the hematologic picture. Previously the rise in hemoglobin content and red cell count resulting from each transfusion of blood had been quickly followed by a rapid fall to anemic levels again. The transfusion given just prior to hospitalization raised the hemoglobin content and the red cell count to high levels, which were exaggerated by dehydration. Reference to table 2 shows that, contrary to previous experience, there was only a slight fall in blood values after this transfusion, when the child was receiving food which it could "handle." These high blood values were permanently maintained.

Factors in the new diet which might have been responsible for the beneficial effect are the protein in the form of amino acids and the brewers' yeast. One must also consider the fact that the previous vomiting was controlled, so that substances necessary for the production of blood were retained in sufficient quantity. The control of vomiting, however, does not seem a likely explanation of the recovery, since infants, even though they may vomit over prolonged periods, do not acquire anemia as a result of this condition. It seems most probable that this infant, due to his severe allergy, was unable to break down the protein offered him, even when that protein was in the form of goat's milk, a food he tolerated much better than cow's milk. However, when the protein was offered in a form in which the amino acids, the building stones for hemoglobin, were present in an assimilable form the anemia was rapidly cured.

The part played by vitamin B, as was mentioned before, is questionable. It is true that after he was admitted to the hospital the baby received and retained large amounts of this vitamin; nevertheless, he had also been receiving it in smaller amounts previously. In my experience I have seen no such prompt cure of anemia by vitamin B.

I do not believe that I have in any way proved that the diet of amino acids cured this infant's anemia. However, the facts seem to me to be extremely suggestive, and I have reported this case in the hope that others will try this same feeding in severe anemias of infancy resistant to treatment with transfusions of blood and with administration of iron. It would be important in an analysis of the relative values of the factors involved to offer the amino acids without the addition of vitamin B, so that the latter factor could be eliminated.

SUMMARY

Nutritional anemia in its wider sense includes much more than anemia due to deficiency of iron. Severely defective formation of hemoglobin in an infant was cured rapidly by the administration of liver. It is possible that certain infants may not be able to construct the hemoglobin molecule because of a metabolic defect. A severely anemic, allergic infant, being fed goat's milk recovered promptly when given a food containing protein in the form of amino acids.

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19. Robscheit-Robbins, F. S.; Miller, L. L., and Whipple, G. H.: J. Exper. Med. **77**:375, 1943.

# SERUM PHOSPHATASE ACTIVITY AND CLINICAL RICKETS IN CHILDREN IN JERUSALEM

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Rickets, which is largely the result of absence of ultraviolet radiation, may be expected to be rare in countries with abundant insolation. However, the data cited by Hess [1] in his book on rickets show that the incidence in some warmer countries is not essentially different from that in northern latitudes. The differences in the diagnostic standards and methods employed and in the age of the children examined make evaluation of the results recorded by various examiners exceedingly difficult. Statements about the prevalence of rickets in the countries of the Near East are few, and opinions about it are divergent. Hitherto the newer and more exact roentgenologic and serologic examinations have not been employed sufficiently in these countries, and, consequently, simple clinical observations have remained the basis of statistics on rickets. In Istanbul, Turkey, Marfan,[2] in 1907, found that rickets occurred frequently, though previous reports had indicated that it was rare there. Caspari [3] (1927) found that it was milder and rarer in Palestine than in Berlin. Shawki [4] (1928) concluded that in Egypt at least 45 per cent and probably 60 per cent of the children between ½ and 2 years of age had rickets. Gruenfelder [5] found an incidence of only 6 per cent in 6,000 children in Jerusalem, but other physicians are of a different opinion. The only fact generally accepted is that severe rickets is rare.

The present investigation was made in order to establish whether the determination of phosphatase activity, supplemented in some instances by roentgen examinations, would aid in the clarification of the data concerning frequency of rickets and relative importance of the milder forms of the disease in Jerusalem. One thousand unselected children ranging in age from ½ to 2½ years were examined as they appeared in the welfare centers [6]; the large majority were from the poorer classes of the Jewish population. The clinical diagnosis "active rickets" was based on craniotabes, rosary and unequivocal swelling of the epiphyses and only exceptionally on such signs as other deformities of the skeleton or muscular weakness. All children were examined independently by two observers, and pathologic conditions observed by both were graded as to severity and were recorded. All determinations of phosphatase activity were performed within six to seven hours after the blood was taken. The exactness of the micromethod employed, Rappaport's modification [7] of A. Bodansky's procedure,[8] was tested by the performance of 98 duplicate examinations. More than half of the duplicate examinations showed differences of less than 3 per cent; the remainder showed differences up to 12.7 per cent (chart 1).

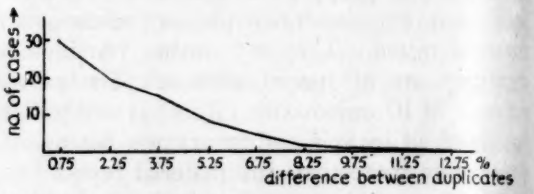


Chart 1.—Reliability of microtechnic used in evaluation of phosphatase activity, as shown by agreement of duplicate examinations.

## CLINICAL SYMPTOMS

Severe active rickets was rare, and only 3 children had multiple signs of active rickets (table 1, line c). A typical rosary was seen only 5 times. Even if all instances of doubtful rosary are included, the total was less than 1.5 per cent. It may be that a racial factor is involved similar

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1. Hess, A. F.: Rickets Including Osteomalacia and Tetany, Philadelphia, Lea & Febiger, 1929.

2. Marfan, A. B.: Maladies des os, Paris, J.-B. Baillière & fils, 1912.

3. Caspari, W.: Jahrb. f. Kinderh. **115**:225, 1927.

4. Shawki, I.: Cong. internat. de méd. trop. et d'hyg., Compt. rend. **2**:961, 1929.

5. Gruenfelder, B.: Personal communication to the author.

6. Dr. Druckmann, head of the X-ray Department of Hadassah University Hospital, Jerusalem, Palestine, made the roentgenologic studies. Dr. Ariely, physician to the Hadassah Infant Welfare Centres, made a parallel examination of each child.

7. Rappaport, F.: Mikrochemie des Blutes, Vienna, Akademische Verlags- und Versandbuchhandlung Emil Haim & Co., 1934, p. 175.

8. Bodansky, A.: J. Biol. Chem. **101**:93, 1933.

to that observed by Hess [1] in relation to swollen epiphyses in Negro children. Since it was assumed that the increase in phosphatase activity could be expected only in children with active rickets, an effort was made to differentiate between patients with healed and with active rickets; but the clinical distinction presents great difficulties when only a single examination is made. Deformities of the skeleton, such as bowed legs, were taken as proof of activity only under exceptional conditions, that is, when the deformities were known to be of recent date or growing worse. In 3 cases rickets was a clinical guess rather than a diagnosis, but the assumption was confirmed by repeated examinations (table 1, line h).

CASE 1.—A boy 8 months old was unable to make spontaneous movements and had severe muscular weakness. The blood plasma contained 4.5 mg. of phosphorus per hundred cubic centimeters, and the phosphatase activity of the serum was 27.5 units per hundred cubic centimeters. After treatment with vitamin D the child began to sit, at the age of 11 months. At 14 months the boy appeared well and began to walk; the anterior fontanel had not yet closed, and the legs were slightly bowed. The level of the blood phosphorus was now 8.2 mg. per hundred cubic centimeters, and the phosphatase activity of the serum was 10.1 units per hundred cubic centimeters.

CASE 2.—A girl 7 months old was in generally good condition, but her occiput was flattened and asymmetric. The child had been born with a normally shaped skull. The phosphorus level of the blood was 4.4 mg. per hundred cubic centimeters, and the phosphatase activity of the serum was 27.2 units per hundred cubic centimeters. The child became dystrophic at the age of 11 to 12 months, and additional signs of rickets appeared. At the age of 17 months she had severe swelling of the epiphyses, Harrison's groove and bowing of the legs. The phosphorus content of the blood was 4.3 mg. per hundred cubic centimeters, and the phosphatase activity of the serum was 33.7 units. The skull remained deformed.

CASE 3.—A girl 11 months old, after having otitis media, was in generally bad condition. She was not able to stand, but there was only an intimation of swelling at the epiphyses. The phosphorus content of the blood was 4.3 mg. per hundred cubic centimeters, and the phosphatase activity was 23.2 units per hundred cubic centimeters of serum. A fortnight later there was distinct swelling of the epiphyses, the phosphorus content of the blood had decreased to 3.5 mg. per hundred cubic centimeters and the phosphatase activity had risen to 28.9 units per hundred cubic centimeters of serum.

All other cases were classified on the basis of the first examination. In 7 cases a tentative diagnosis was finally corroborated by roentgen examination (table 1, line i, and table 2).

Of the 1,000 children examined, 55 had active rickets, most of them a mild form. The high incidence of craniotabes (in 17 children out of 55) raises the question as to how far age, sex and season influence this condition. There was a slightly higher incidence among boys, 6 per cent as against 5 per cent among girls; but the difference is so small that it may be accidental. In view of the small number of cases of active rickets, the percentages found in the different age groups can have no claim to validity. The figures are: Six to 12 months, 8.6 per cent; 12 to 18 months, 5.4 per cent; 18 to 24 months, 0.9 per cent, and 24 to 30 months, 2.7 per cent. Since about a quarter of the children (234) were examined during the three winter months, the winter peak of active rickets does not unduly influence the calculated incidence. The result of the clinical examination is to be stated as 5.5 ± 3.0 (3 times the standard error of the difference), equal to between 3.3 and 7.7 per cent active rickets among children 6 to 30 months of age.

TABLE 1.—*Correlation Between Clinical Signs of Rickets and Phosphatase Activity*

| | Number of Times Each Clinical Sign Observed | | | | | | | | | | | | Means | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Craniotabes | | | Swollen Epiphyses | | | Rosary | | | Bases of Diagnosis of Active Rickets | | | Phosphatase Activity, Bodansky Units | Phosphorus, Mg. per 100 Cc. | |
| | ++ | + | ± | ++ | + | ± | ++ | + | ± | | | | | | |
| a | 5 | .. | .. | .. | .. | 2 | .. | .. | .. | Craniotabes..... | ++ | 5 | 24.62 | 4.76 | a |
| b | .. | 11 | .. | .. | .. | 2 | .. | .. | .. | | + | 11 | 21.90 | 5.50 | b |
| c | .. | 1 | .. | 6 | .. | .. | 1 | 1 | 1 | Swollen epiphysis | ++ | 6 | 33.50 | 4.25 | c |
| d | .. | .. | .. | .. | 15 | .. | .. | .. | .. | | + | 15 | 20.70 | 5.74 | d |
| e | .. | .. | .. | .. | .. | .. | .. | .. | .. | Rosary..... | ++ | .. | ..... | .... | e |
| f | .. | .. | .. | .. | .. | .. | .. | 3 | .. | | + | 3 | 18.00 | 5.33 | f |
| g | 5 | 12 | .. | 6 | 15 | 4 | 1 | 4 | 1 | Total..... | | 40 | 23.18 | 5.27 | g |
| h | .. | .. | .. | .. | .. | 1 | .. | .. | .. | Other clinical signs..... | | 8 | 26.16 | 5.00 | h |
| i | .. | .. | .. | .. | .. | 1 | .. | .. | .. | Roentgen examination.... | | 7 | 20.46 | 5.80 | i |
| j | 17 | | | 21 | | | 5 | | | Total..... | | 55 | 23.28 | 5.27 | j |

## SERUM PHOSPHATASE ACTIVITY

To begin with, it was necessary to determine the limits of the "normal" phosphatase activity. In the literature the limit between normal and augmented values is given as about 10 to 14 Bodansky units, but recently Barnes and Munks [9] pointed out that normal values for phosphatase

9. Barnes, D. J., and Munks, B.: Proc. Soc. Exper. Biol. & Med. **44**:327, 1940.

TABLE 2.—*Roentgenologic Classification, Clinical Signs and Phosphatase Activity*

| | Number | Age, Mo. | Phosphatase Activity | Swollen | | | Deformed | | | History of Rickets or Rachitic Signs | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Craniotabes | Epiphyses | Rosary | Head | Chest | Legs | | |
| **Roentgenologic Classification: Active Rickets** | | | | | | | | | | | |
| Severe | 399 | 16* | 65 | + | +++ | +++ | ++ | — | .. | 7 mo.: craniotabes | |
| | 419 | 15* | 55 | .. | +++ | + | .. | + | .. | 9 mo.: rosary | |
| | 507 | 8† | 23 | .. | ± | .. | .. | .. | .. | 5 mo.: craniotabes | 14 days of vitamin D therapy at 8½ mo. |
| | | 14 | 14 | .. | ± | .. | .. | + | ++ | ..... | Started to walk |
| | | 15 | 11 | .. | ± | .. | .. | + | ++ | | |
| Moderate | 398 | 24* | 30 | .. | .. | .. | .. | .. | .. | ..... | Dystrophic, unable to stand |
| | 485 | 10* | 20 | + | .. | .. | .. | .. | .. | ..... | Unable to stand |
| | | 17 | 10 | .. | .. | .. | .. | + | .. | ..... | Began to walk when 12 mo. old |
| | 488 | 10* | 22 | + | .. | .. | .. | .. | .. | ..... | Dystrophic, unable to sit |
| | | 17 | 12 | .. | .. | .. | .. | .. | .. | ..... | Dystrophic, started to walk |
| | 489 | 6* | 30 | .. | .. | .. | .. | .. | .. | ..... | |
| | | 8 | 16 | .. | .. | .. | .. | .. | .. | ..... | |
| | 513 | 19* | 15 | .. | .. | .. | .. | .. | .. | ..... | Dystrophic, hardly able to stand |
| | | 26 | 7 | .. | .. | .. | .. | .. | .. | ..... | Dystrophic, began to walk when 25 mo. old |
| Slight | 401 | 12* | 13 | .. | .. | .. | .. | .. | .. | ..... | Dystrophic, unable to stand |
| | | 19 | 10 | .. | .. | .. | .. | .. | .. | ..... | Dystrophic, began to walk when 17 mo. old |
| | 447 | 10* | 14 | .. | .. | .. | .. | .. | .. | ..... | Unable to sit |
| | 480 | 10* | 10 | .. | + | .. | .. | .. | .. | ..... | |
| | 568 | 9* | 19 | .. | .. | .. | .. | .. | .. | ..... | |
| **Roentgenologic Classification: Healed Rickets** | | | | | | | | | | | |
| Severe | 58 | 20 | 9 | .. | .. | .. | .. | .. | +++ | 11 mo.; genu varum † | |
| | | 24* | 9 | .. | .. | .. | .. | .. | +++ | ..... | |
| | 242 | 16 | 12 | .. | ++ | ± | + | .. | .. | 8 mo.: rickets | 9 to 10 mo.: vitamin D therapy |
| | | 17 | 7 | .. | ++ | .. | + | .. | .. | ..... | 17 to 20 mo.: ultraviolet treatment |
| | | 19* | 12 | .. | ± | .. | + | .. | .. | ..... | |
| | | 25 | 8 | .. | .. | .. | .. | .. | + | ..... | |
| Moderate | 427 | 12* | 13 | .. | ± | .. | .. | .. | + | ..... | |
| | 428 | 19* | 10 | .. | ± | .. | .. | .. | + | 13 mo.: rickets | Since 17 mo.: vitamin D therapy |
| Slight | 9 | 13 | 20 | .. | .. | .. | .. | .. | .. | ..... | Excellent development |
| | | 15* | 16 | .. | .. | .. | .. | .. | .. | ..... | 8 to 14 mo.: vitamin D therapy |
| | | 17 | 13 | .. | .. | .. | .. | .. | .. | ..... | |
| | 33 | 13 | 9 | .. | .. | .. | .. | + | .. | ..... | Began to walk when 12 mo. old |
| | | 19* | 12 | .. | ± | .. | .. | + | .. | ..... | |
| | 429 | 8* | 11 | .. | .. | .. | .. | .. | .. | ..... | Fat infant |
| **Roentgenologic Classification: No Signs of Rickets** | | | | | | | | | | | |
| Phosphatase > 15 units | 470 | 6* | 20 | .. | .. | .. | .. | .. | .. | ..... | Fat infant |
| | | 9 | 8 | .. | .. | .. | .. | ++ | .. | ..... | Unable to sit |
| | 472 | 7* | 22 | .. | .. | .. | .. | .. | .. | ..... | |
| | | 14 | 18 | .. | .. | .. | .. | .. | + | 11 mo.: genu varum | |
| | 486 | 24* | 47 | .. | .. | .. | .. | .. | .. | ..... | Stunted growth ‡ |
| | 510 | 20* | 17 | .. | .. | .. | .. | .. | .. | ..... | Fontanel 4 × 4 cm., no hydrocephalus |
| | 512 | 19* | 21 | .. | .. | .. | .. | .. | .. | ..... | |
| Phosphatase < 15 units | 28 | 17* | 11 | .. | ± | .. | .. | + | .. | ..... | |
| | | 22* | 8 | .. | ± | .. | .. | + | .. | ..... | |
| | 432 | 7 | 8 | .. | .. | .. | + | .. | .. | ..... | Fontanel 3 × 4 cm. |
| | | 8* | 11 | .. | .. | .. | + | .. | .. | ..... | |
| | 475 | 6* | 13 | .. | ± | .. | .. | .. | .. | ..... | |
| | 487 | 17* | 14 | .. | .. | .. | .. | .. | .. | 5 mo.: craniotabes | Dystrophic, unable to stand |
| | 499 | 23* | 12 | .. | ± | .. | .. | .. | .. | ..... | Dystrophic |
| | 506 | 8* | 14 | .. | ± | .. | .. | .. | .. | ..... | |
| | | 10 | 12 | .. | ± | .. | .. | .. | .. | ..... | Unable to sit |
| | | 15 | 13 | .. | ± | .. | .. | + | .. | ..... | Unable to walk |
| | 509 | 9* | 12 | .. | .. | .. | .. | .. | + | ..... | |
| **Controls** | | | | | | | | | | | |
| | 471 | 17* | 14 | .. | .. | .. | .. | .. | .. | ..... | Began to walk when 16 mo. |
| | 473 | 23* | 10 | .. | .. | .. | .. | .. | .. | ..... | |
| | 477 | 24* | 7 | .. | .. | .. | .. | .. | .. | ..... | |
| | 478 | 11* | 12 | .. | .. | .. | .. | .. | .. | ..... | |
| | 482 | 20* | 9 | .. | .. | .. | .. | .. | .. | ..... | |
| | 484 | 12* | 8 | .. | .. | .. | .. | .. | .. | ..... | Dystrophic, unable to stand |
| | 502 | 22* | 13 | .. | .. | .. | .. | .. | .. | ..... | |
| | 508 | 19* | 7 | .. | .. | .. | .. | .. | .. | 14 mo.: rickets | Fontanel not yet closed |

* Roentgenogram made within 1 to 4 days.
† Roentgen examination revealed, besides signs of an old healed rickets, signs of a milder episode just healing.
‡ Roentgen examination revealed severe decalcification, not of the type seen in rickets.

activity in children have not been established with accuracy. The ages of the children in the different investigations varied, and it is also not known how far racial and geographic factors influenced the "normal" values. To eliminate possible sources of error, only healthy, well developed children who were free of all signs of rickets were taken for the determination of the normal value. Of 1,000 children 320 could be regarded as normal controls. The mean value of phosphatase activity in these healthy children between ½ and 2½ years of age was 9.409 units ± 2.796, and the normal range was 5.59 to 15.0 units. This is approximately the range of twice the standard deviation, which in an ideal curve of distribution includes 95.6 per cent of all measurements. In our series 97 per cent of the 320 determinations fall within this range. Sex and age do not influence the result; the differences of the means of the phosphatase activity of the corresponding groups lie within three times the standard errors of the differences. For the sake of brevity only the means for all the 1,000 children are given here: Five hundred and nineteen boys, 10.47 units; 481 girls, 9.91 units; all children 6 to 11 months old, 10.86 units; children 12 to 17 months old, 10.59 units; children 18 to 23 months old, 9.25 units, and children 24 to 30 months old, 9.32 units.

Absolute agreement between diagnoses based on the values for phosphatase and on the clinical examinations cannot be expected if one considers the difficulties of clinical definition of active rickets. Unfortunately the roentgen examinations had to be suddenly curtailed because of the cost and the scarcity of the materials. Nevertheless the 39 pictures taken aided in establishing the correlation between variations in phosphatase activity and the different types of rickets. Rickets was evident clinically or by roentgen examination without a corresponding increase in phosphatase activity in 5 patients (table 2, patients 401, 447, 480 and 442, and a patient, not listed in the table, who had craniotabes with 12.9 units of phosphatase activity per hundred cubic centimeters of serum). Patients 401 and 447 can be regarded as having mild rickets. The roentgenogram of patient 242, taken when the child was 16 months old, does not reveal whether the rickets was active at that time; swelling of the epiphyses was present, but this symptom may be more pronounced during convalescence, as Hess[1] observed.

There was pronounced parallelism between severity of symptoms and increase of phosphatase activity (table 1, a), but the number of cases was too small to permit of definite conclusions. This parallelism of the phosphatase activity to the course of the illness may be seen in the records of the cases of most severe rickets in the series.

Case 4.—The patient (399, table 2) came from the poorest surroundings; the mother was unable to bring the child for treatment with ultraviolet rays. At the age of 7 months the child had craniotabes and at 9 months he had other signs of rickets. From the time the patient was 7 months old vitamin D was given irregularly. Severe dystrophy was evident when the child was 9 months old. At the age of 16 months the child came under my observation. The clinical and laboratory data for the period from March 31 to September 16 were:

| Date | Phosphorus, Mg./100 Cc. | Phosphatase Units | Fontanel, Cm. | Craniotabes | Swollen Epiphysis | Rosary | Deformed: Head | Deformed: Chest | Deformed: Legs |
|---|---|---|---|---|---|---|---|---|---|
| Jan. 31 | 3.4 | 65.0 | 2 × 4 | + | +++ | +++ | ++ | + | — |
| Feb. 25 | 2.2 | 33.4 | 2 × 3 | ± | ++ | ++ | ++ | + | — |
| Mar. 4 | 4.6 | 45.7 | 2 × 3 | ± | ++ | ++ | ++ | + | — |
| Mar. 6 | 3.6 | 43.6 | 2 × 3 | ± | ++ | ++ | ++ | + | — |
| Mar. 13 | 4.0 | 40.6 | 2 × 3 | — | ++ | + | ++ | + | — |
| Mar. 24 | 4.5 | 36.3 | 2 × 3 | — | ++ | + | ++ | + | — |
| Mar. 31 | 4.7 | 42.3 | 2 × 2 | — | ++ | + | ++ | +++ | — |
| May 21 | 4.7 | 36.1 | 2 × 2 | — | ++ | ± | ++ | +++ | — |
| Sept. 16 | 5.1 | 34.8 | 2 × 2 | — | ++ | ± | ++ | +++ | + |

Case 5.—The social status of the parents of this patient (419, table 2) was good, and the child was well cared for. From the time the infant was 8 months old additional vitamin D was given. The general development was poor, particularly during the second year. While the patient was 15 to 23 months old the clinical and laboratory data were:

| Date | Phosphorus, Mg./100 Cc. | Phosphatase Units | Fontanel, Cm. | Craniotabes | Swollen Epiphysis | Rosary | Deformed: Head | Deformed: Chest | Deformed: Legs |
|---|---|---|---|---|---|---|---|---|---|
| Feb. 7 | 3.9 | 54.5 | 3 × 4 | — | +++ | + | — | + | — |
| Mar. 6 | 3.7 | 50.2 | 3 × 3 | — | ++ | + | — | + | — |
| Mar. 13 | 4.1 | 46.7 | 3 × 2 | — | ++ | + | — | + | — |
| Mar. 24 | 3.9 | 40.0 | 3 × 2 | — | + | ± | — | + | — |
| May 8 | 3.7 | 41.6 | 1 × 2 | — | + | — | — | ++ | — |
| July 24 | 6.7 | 24.2 | Closed | — | + | — | — | ++ | — |
| Sept. 11 | 6.7 | 21.6 | Closed | — | ± | — | — | ++ | — |
| Oct. 9 | 6.0 | 14.7 | Closed | — | — | — | — | — | — |

It appears from the results listed in table 3 that, except in a few cases, active rickets is accompanied by an increase in the phosphatase

Table 3.—*Correlation Between Phosphatase Activity and Active Rickets*

| Phosphatase Activity, Bodansky Units | Patients with Active Rickets: Known % | Known No. | Probable % | Probable No. | Total, % | Not Known % | Not Known No. |
|---|---|---|---|---|---|---|---|
| >20 | 77 | 35 | 9 | 4 | 86 | 14 | 6 |
| 15-20 | 40 | 17 | 24 | 10 | 64 | 36 | 15 |
| Total > 15 | 59 | 52 | 16 | 14 | 75 | 25 | 21 |
| 12.5-15 | 3.5 | 3 | 3.5 | 3 | 7 | 93 | 80 |
| <12.5 | 0.2 | 2 | .. | .. | 0.2 | 99.8 | 827 |
| Total < 15 | 1.9 | 5 | 1.8 | 3 | 7.1 | 96.4 | 907 |

activity of the serum. The converse, that increased phosphatase activity occurs in active rickets only, is not equally evident from the results of this investigation. In 3 patients an increase in the phosphatase activity was due to other disturbances. Two of these 3 had jaundiced serum without clinical manifestation of jaundice. (One child was extremely dystrophic and no reexamination could be made; the other was feeling well all the time. In the latter patient the phosphatase activity dropped from 21.2 units to 7.5 units in a fortnight.) The observed discoloration of the serum suggests some slight and transient hepatic damage. Such a condition might be expected in dystrophic children rather than in healthy ones, whereas, actually, increased phosphatase activity without clear signs of rickets was three times as frequent in healthy as in dystrophic children. Disturbances of the skeletal system, as in patient 486, in whom the roentgenogram showed serious decalcification only, are exceptions. In view of the small proportion of subjects for whom roentgenograms were made, one can only surmise that additional cases might have been verified by further use of this means of diagnosis. On the other hand, in some instances a diagnosis of rickets based on the increase of phosphatase activity was not corroborated by roentgen examination (470 to 512, table 2). Analysis of the history of patient 472 makes it appear probable that the increased phosphatase activity was the first sign of rickets. It was possible in the cases of 14 patients with increased phosphatase activity but dubious clinical signs at the first examination to relate the increase to active rickets by means of reexaminations. These 14 patients were selected more or less by chance, if and when reexaminations could be made within a reasonable time. The mean value for phosphatase activity in this group was 16.8 units. The data for the remaining 21 patients were not so significant in the statistical evaluation of the phosphatase determination. If it is assumed that phosphatase activity of more than 15 units represents active rickets, then there were 88 such cases in the 1,000 studied, an incidence of 8.8 per cent. The clinical and roentgenologic examination, however, revealed an incidence of only 5.5 per cent. The difference, 3.3 per cent, still remains within the range of three times the standard error of the difference and might therefore have been accidental.

$$d = 3.3;\ \text{S.E.D.} = \sqrt{\text{S.E.}5.5^2 + \text{S.E.}8.8^2}$$

$$= \sqrt{0.51975 + 0.80256} = 1.15;\ d = 3.3 < 1.15 \cdot 3$$

In view of the analysis of the individual cases, the concordance between 8.8 per cent and 5.5 per cent is not an accident. Increased phosphatase activity and clinical signs are manifestations of the same disturbance, albeit the determination of phosphatase activity seems to be more sensitive and is sometimes difficult to interpret. It is not possible to work out a coefficient of correlation between phosphatase activity and active rickets because the influence of the 827 "negative cases" (phosphatase activity below 12.5, no clinical rickets) would mask the result.

Since the number of cases of clinical rickets is small, according to probabilities, the agreement in another series of examinations might be expected to have any value between 61 and 89 per cent. The percentage found here corresponds well with the correlation of 65 per cent in 187 children reported by Barnes and Carpenter,[10] in one of the few statements on this subject found in the literature.

Though the result of the determination of the phosphatase activity cannot with certainty be applied to the diagnosis in an individual case, the test is of value as indicated by the following considerations:

1. Unequivocal swelling of the epiphyses is accompanied almost without exception by an increase in the phosphatase activity of the serum.

2. Normal phosphatase activity in the presence of swollen epiphyses indicates a state of healing.

3. Indefinite changes in the epiphyses are, in most instances, not a sign of active rickets but of a healed condition or some other abnormality. (The mean value for phosphatase activity in all 36 such cases in this series was 10.77 units, and roentgenograms also showed no active rickets.)

4. When increased phosphatase activity is present with insufficient or completely lacking clinical indications of rickets, a roentgenogram or repeated determinations of the phosphatase activity will show rickets as the cause.

5. The phosphatase activity of the serum remains high throughout the period of active rickets; the decrease to normal values coincides fairly well with clinical recovery, while increased value for phosphatase activity may precede the first clinical symptoms.

It may be added at this point that the determination of phosphorus in the serum, which is automatically performed in the course of the determination of phosphatase activity, is a much less reliable diagnostic aid. Only in clinically severe rickets, in which no further diagnostic aids are needed, was the phosphorus content of the plasma constantly low. Most patients with rickets, however, had completely normal values

10. Barnes, D. J., and Carpenter, M. D.: J. Pediat. **10**:596 (May) 1937.

for phosphorus, and the majority of patients with low values had no signs of rickets.

Whereas no significant differences in the phosphatase activity in relation to sex and age could be found, the influence of the seasons is obvious. The high intensity of ultraviolet irradiation in Jerusalem as compared with the intensity in other geographic locations is indicated in chart 2 *A*, and the seasonal variations in the incidence of active rickets, in chart 2 *B*. The mean and the range of phosphatase activity (range, three times the standard error of the mean) for each of the seasons is shown in chart 2 *C*. Though the means for the 625 children with poor development and doubtful signs of rickets (the cases of proved active rickets are of course excluded) are somewhat higher than the means of the "controls," the differences, viewed mathematically, are without importance. But the sudden rise in phosphatase activity in winter and the decrease in the fall are significant in both groups. Although the determination of the phosphatase activity can be regarded only as an indirect test for vitamin D, these statistical differences point to a climax of saturation with vitamin D at the end of the summer and to a relative lack during winter, even in children without any signs of rickets.

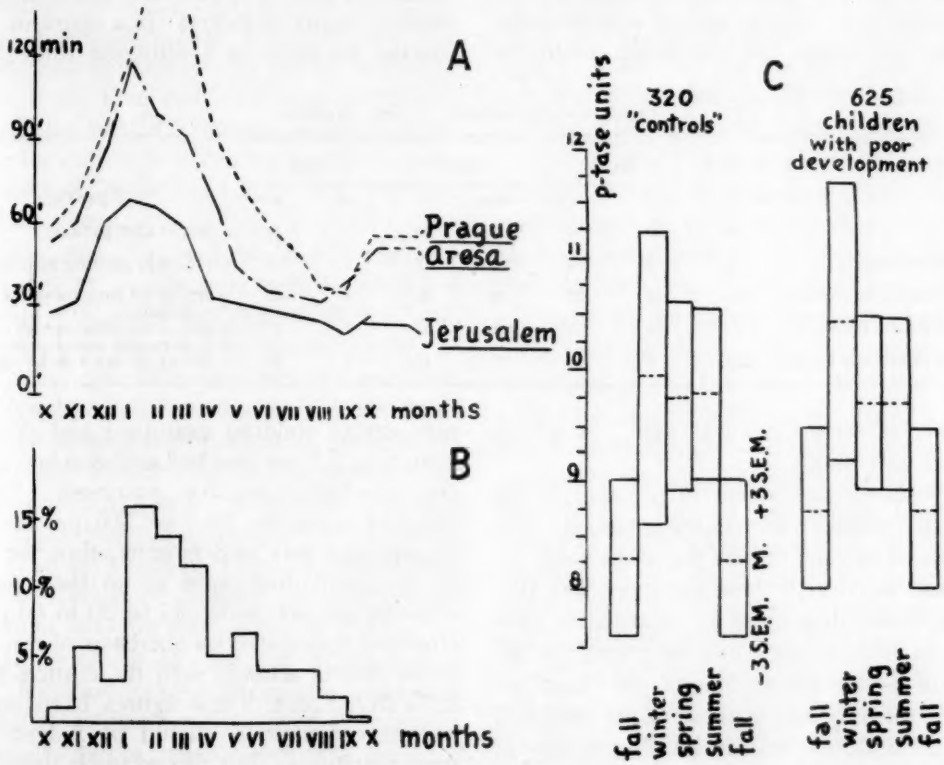


Chart 2.—Relation of the intensity of ultraviolet irradiation to the incidence of active rickets and to seasonal variations in the phosphatase activity. *A*, comparison of the intensity of ultraviolet irradiation at different places, expressed as minutes of exposure to sunshine at midday necessary to cause an erythema. *B*, seasonal distribution of cases of active rickets in Jerusalem. *C*, seasonal variations in the mean value for phosphatase activity in the children studied. (*M* indicates the mean; *S. E. M.* indicates the standard error of the mean.)

### DIAGNOSTIC VALUE OF SKELETAL DEFORMITIES

During this investigation so many conditions were encountered which might be connected with rickets that the value of some "signs of rickets" should be discussed briefly. The diagnostic value of craniotabes and of the changes at the epiphyses was shown by comparison with the level of phosphatase activity, but the other signs may be residuals of a process long healed or may have no connection with rickets. Rickets is often diagnosed on the presence of an open fontanel, although the mechanism of the origin of this condition and its persistence after healing of the rickets are not fully understood. Moreover, the data as to when the fontanel should normally be closed are not uniform. Of 92 instances of distinct delay, only 29 could be related with more or less certainty to rickets. In the same way, the development of the static functions is not especially helpful in the diagnosis of rickets; the best criterion of this type was the age at which the child began to walk without help. Naturally, children suffering from active rickets begin to

walk later than normal children. However, among normally developed children there are many "late walkers." Any disease which results in insufficient gain in weight produces the same delay as active rickets. The correlation between development of weight and begining of walking was $0.73 \pm 0.016$ (282 cases). Thus late walking is not a reliable single criterion for the diagnosis of active rickets.

The deformities of the skeleton, such as caput quadratum and genu varum are considered classic symptoms, as are the changes at the epiphysial lines. Deformity of the chest was usually confined to a slight but distinct bending of the lower ribs; in 5 patients we observed a true pectus carinatum. Genu varum was recorded only when the knees did not touch when the ankles did; severe varum was rare. A gibbus was found only twice.

Table 4 shows that about 90 per cent of the skeletal deformities are unaccompanied with other signs of rickets. Since the mean value for phosphatase activity in these instances was 10.0 units, the deformities must be regarded as residual. A rachitic origin could be traced for the majority of severe deformities of the chest and of the legs, for only half of those of the skull and for 8 of 27 multiple deformities. Since one of the observers, Dr. Ariely, treated the children during the whole period of infancy, the uniformity of the diagnostic standard has been safeguarded. Rachitic conditions may have occurred in some patients without having been recorded in the course of routine examinations, and for 62 of the 1,000 subjects of this study a reliable anamnesis could not be found. However, the incompleteness of the anamnesis cannot explain the surprising fact that of 168 patients with skeletal signs rickets or deformities had been known before in only 42. On the other hand, of a total of 128 children with a positive history of rickets only the same 42 children still had residual deformities a few months later.[11] Deformities of the chest may result from bronchitis, and bowed legs are at times probably caused by early walking; an explanation for the nonrachitic origin of the caput quadratum is lacking. Except in severe rickets no clinical distinction seems possible between rachitic and nonrachitic deformities. It cannot be decided here how frequent the latter are and whether part of them may be simple anatomic variations; but, obviously, a rate of incidence of rickets based on skeletal "signs of rickets" is a spurious one. A concise summary will illustrate this: Nineteen per cent of children examined had skeletal deformities; 5.5 per cent had active rickets, and 14.3 per cent had a positive anamnesis. Excluding identical cases the total is 27.6 per cent. The average age was 14.8 months; thus the chances for the individual child up to the age of 2½ years to get rickets would be 50 to 60 per cent. However, calculated on the basis of the cases of active rickets actually seen the chances are only 22 to 28 per cent. These figures, based on mathematical calculations, should be judged as only approximations. But this example demonstrates well that statements on the incidence of rickets without distinction between active rickets and healed rickets and without definition of the diagnostic standards employed only add to the confusing data which Hess described as "the most remarkable hodge-podge of statistics that is to be found in relation to any disorder."

TABLE 4.—*Deformities of the Skeleton*

| | Number of Patients | Head | | Chest | | Legs | | Per Cent |
|---|---|---|---|---|---|---|---|---|
| | | ++ | + | ++ | + | ++ | + | |
| Total | 190 | 20 | 66 | 9 | 70 | 7 | 51 | = 19% of 1,000 patients |
| Patients with active rickets | 22 | 6 | 6 | 1 | 7 | 3 | 6 | = 40% of 55 patients with active rickets |
| Patients without active rickets | 168 | 14 | 60 | 8 | 63 | 4 | 45 | = 18% of 945 patients without active rickets |
| Previous rickets known | 42 | 5 | 15 | 5 | 16 | 3 | 12 | = 25% of 168 patients with skeletal deformities without active rickets |
| Previous rickets not known | 126 | 9 | 45 | 3 | 47 | 1 | 33 | = 75% of the same 168 patients |

11. These 128 children should not be confused with the 126 children in table 4; the similarity of the numerical values is a chance occurrence.

# CYSTIC FIBROSIS OF THE PANCREAS

## REPORT OF EIGHTEEN PROVED CASES

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The essential lesion of the disease now known as cystic fibrosis of the pancreas has been seen by pathologists for many years, but it was not until Andersen [1] in 1938 correlated the pancreatic changes with the development of steatorrhea and pneumonia that the condition was recognized as a definite clinical entity. Children suffering from this condition show clinically failure to gain weight, wasting, vomiting, diarrhea or constipation, protuberant abdomen, bulky fatty intestinal contents, cough and terminal bronchopneumonia.

Andersen first reported 27 cases from the literature and 22 cases from records of necropsies at the Babies Hospital in New York. A total of 123 cases was reported by August 1943. In only a few of the 123 cases was the condition diagnosed ante mortem, and in only 3 was treatment attended with any measure of success. A comprehensive bibliography of the previous reports is included in a recent survey by Wolman.[2] In a recent article on pancreatic insufficiency, an additional 52 cases in which autopsies were obtained at Children's Hospital in Boston from 1937 to 1942 inclusive were listed by Farber.[3]

We are reporting 18 cases in which diffuse definite dilatation of the pancreatic acini and associated pneumonia were observed at necropsy. Also included is the brief history of a child for whom a clinical diagnosis of cystic fibrosis of the pancreas was made, who was treated in the Children's Hospital in Pittsburgh.

The salient clinical features of the 18 cases in which autopsies were obtained are presented in the table. Additional data are summarized as follows: All the patients were of full term gestations; 16 were white and 2 were Negro; they came of Italian, German, Irish, English, Scotch and American stock; all but 2 were born into families of average or better than average circumstances; the mother of patient B. H. (case 7) was syphilitic, and a sibling of patient J. A. F. (case 12) did not gain weight properly and died of pneumonia during infancy; otherwise the family histories were essentially normal.

Most of the children were started on breast feeding, but in only 6 instances was this maintained totally or partially for more than a week. Many preparations for artificial feeding were tried, but they were uniformly unsuccessful.

Several of the patients showed slight albuminuria, mild anemia and mild to moderate leukocytosis. Patient C. M. S. (case 10), however, had a white cell count of 89,900 per cubic millimeter. The concentration of cholesterol in the blood of patients V. H. (case 8) and J. A. F. (case 12) was 120 and 126 mg. per hundred cubic centimeters of blood respectively. A "flat" dextrose tolerance curve was obtained for patient B. W. (case 11). The albumin-globulin ratio was normal in patients B. W. (case 11) and J. A. F. (case 12) but was reversed, with the total protein ranging from 5.5 to 9.8 per cent, in patient M. E. M. (case 15). Stools from patient J. A. F. (case 12) contained an excessive amount of fat. Stools from patient B. W. (case 11) contained 60 to 70 per cent fat by dry weight, less than 1 per cent of which was present as "split" fat. The Kahn reaction of the serum of patient B. H. (case 7) was positive; 8 other patients had negative reactions.

Diagnostic bronchoscopies were performed on patients J. K. (case 6), C. M. S. (case 10) and B. W. (case 11). In patient J. K. (case 6) no pus was seen in the trachea down to the bifurcation, and the trachea was reported to be normal. In the other 2 children, however, thick mucopurulent material was aspirated from the trachea, and the mucosa was reddened and appeared to be much thickened. In patient B. W. (case 11)

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1. Andersen, D. H.: Cystic Fibrosis: Relation to Celiac Disease; a Clinical and Pathologic Study, Am. J. Dis. Child. **56**:344-399 (Aug.) 1938.

2. Wolman, I. J.: Cystic Fibrosis of the Pancreas, Am. J. M. Sc. **203**:900-906 (June) 1942.

3. Farber, S.: Pancreatic Insufficiency and the Celiac Syndrome, New England J. Med. **229**:653-657 (Oct. 21) 1943.

the lumen of the left main stem bronchus was reduced to about one-third normal size.

Therapeutic measures consisted, for the most part, of alterations in the feeding formula and maintenance of the body fluids. Transfusions of plasma and whole blood were given to 5 of the patients. A number of children received one or more of the sulfonamide drugs. Vitamin concentrates were also frequently given, usually in the average therapeutic doses. Pancreatin, 0.5 to 1 Gm. in each feeding, was given to patient B. W. (case 11) for one month without producing any appreciable change in the child's condition.

Roentgenograms of the chest, taken for all but 3 of the patients, showed a remarkable similarity, except those of the 2 oldest children. There was an unusual enlargement of the hilar shadows, and a bilateral shadow was present, decreasing toward the periphery.

The extent of pancreatic involvement in each patient is noted in the table. Grossly, the pancreas appeared normal, except for a slightly increased resistance on sectioning, in all but 1 patient. An attempt to dissect out the ducts of the pancreas of patient C. M. S. (case 10) disclosed that the duct of Wirsung was stenosed to less than 1 mm. in diameter, while the duct of Santorini appeared normal. Microscopically, there were diffuse lesions which involved various amounts of acinar tissue. The acini and smaller ducts had dilatations varying from barely perceptible enlargements to cysts that were grossly visible. The lumens contained various amounts of eosin-stained material, appearing either as a solid homogeneous mass or as a collection of coarser granules in a fine, granular matrix. Macrophages were observed in some of the dilated ductules, and in others an occasional neutrophil or lymphocyte was seen. Proportionate to the dilatation, there was flattening of the ductular and acinar epithelium with actual destruction in some places. A reduction in the number of acini frequently occurred. Interlobular and intralobular connective tissue was increased to some extent in all sections, predominated in a few and contained scattered lymphocytes and plasma cells. The islet tissue was essentially normal in all sections.

The liver showed little gross abnormality, except enlargement in a few instances. In patient M. E. M. (case 15) this organ was mottled with small cream-colored areas, and in patient C. S. (case 2) a small abscess was observed at the hilus. The bile ducts were patent in all instances; however, in patient N. C. (case 5) an anomaly of the common bile duct was noted which may have been a possible source of intermittent obstruction. In the same patient a great increase of fibrous tissue occurred around the portal triad and intralobularly, but the hepatic bile ducts appeared to be normal. In patient J. P. (case 1) the bile ducts were involved in a biliary cirrhosis. Fatty infiltration and early central necrosis were occasionally noted. In patients C. M. S. (case 10), J. A. F. (case 12) and P. S. (case 17) there was no microscopic evidence of hepatic damage.

Grossly, the lungs showed bronchopneumonia in all of the patients and definite abscesses in several of them. Microscopically, the lesion was essentially bronchitis, bronchiolitis and peribronchiolitis. The lumens of the bronchi and bronchioles were densely infiltrated with neutrophils, and this infiltration often extended into the surrounding alveolar tissue to form areas of consolidation containing neutrophils and occasionally fibrin and red blood cells. Typical abscesses frequently occurred in such areas, and in places the wall of the bronchus was eroded. Squamous metaplasia of the tracheal and bronchial epitheluim was noted in patients B. W. (case 11), J. A. F. (case 12), T. B. (case 13) and P. S. (case 17).

The essential data in the case of J. T., the patient treated for cystic fibrosis of the pancreas, are as follows:

The patient was a 22 month old, poorly developed, malnourished white girl. The family history was normal. She weighed 6½ pounds (2,950 Gm.) at birth and appeared to be normal for the first five months; then a cough developed which gradually grew worse and was accompanied by vomiting and raising of a yellow mucopurulent material. At the end of five months she weighed 13 pounds (5,900 Gm.) and during the next seventeen months gained only 3 pounds (1,300 Gm.). She was breast fed for four months; then for eight months she was given diluted condensed milk and sucrose and for the next ten months varying concentrations of cow's milk and dextrimaltose. Cod liver oil and orange juice were administered in adequate amounts. The patient was admitted to the hospital July 2, 1943 with abdominal distention and pain of seventeen months' duration and with grunting respiration except when sleeping. The child had never stood or walked of her own accord but sat up and dragged herself along the floor.

The physical abnormalities included generalized muscular hypoplasia, especially in the muscles of the leg, but there were no neurologic symptoms. The skeletal development at the wrist was that of a child of 6 months. The lower lobes of the lungs were somewhat dull on percussion. Roentgenograms of the chest showed obvious hilar density and bilateral shadows diminishing

| Patient | Case | Sex | Age on Admission to Hospital | Weight on Admission, Lb. | Time of Onset of Symptoms | Chief Symptoms: Vomiting | Diarrhea | No Gain in Weight | Loss in Weight | Cough | Stridor | Dyspnea | Physical Signs | Bacterial Cultures | Nature of Pancreatic Lesions: Cystic | Nature of Pancreatic Lesions: Fibrotic | Lesions Other Than in Pancreas |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Group A** | | | | | | | | | | | | | | | | | |
| J. P. | 1 | M | 3 days | .... | Birth | + | .. | + | .. | .. | .. | .. | Abdominal distention, high intestinal obstruction | ..... | Moderate | Moderate | Atresia of jejunum, peritonitis |
| **Group B** | | | | | | | | | | | | | | | | | |
| C. S. | 2 | M | 21 days | .... | Birth | + | .. | + | .. | .. | .. | .. | Abdominal distention, jaundice, pyoderma | ..... | Moderate | Moderate | Peritonitis |
| M. K. | 3 | M | 25 days | .... | Birth | .. | .. | .. | .. | + | + | + | Dulness and partial collapse of right lung | ..... | Severe | Moderate | |
| M. A. W. | 4 | F | 81 days | 6.9 (3,130 Gm.) | Birth | .. | .. | .. | + | .. | .. | .. | Ecchymosis of skin, jaundice | Blood: Staph. aureus | Severe | Moderate | |
| N. C. | 5 | F | 3 mo. | 6.3 (2,860 Gm.) | Birth | .. | + | + | .. | .. | .. | .. | Abdominal distention, cyanosis, rales | Throat: Staph. aureus | Moderate | Moderate | |
| J. K. | 6 | M | 3 mo. | 8.5 (3,863 Gm.) | Birth<br>3 wk. | +<br>.. | +<br>.. | +<br>.. | ..<br>.. | ..<br>+ | ..<br>+ | ..<br>.. | Bronchovesicular breathing | Bronchoscopic mucus: negative | Severe | Severe | |
| B. H. | 7 | F | 3 mo. | 6.5 (2,950 Gm.) | Birth<br>10 wk. | ..<br>+ | ..<br>.. | ..<br>.. | ..<br>.. | ..<br>.. | +<br>.. | +<br>.. | Bronchopurulent nasal discharge, rales | ..... | Moderate | Slight | |
| V. H. | 8 | F | 3.5 mo. | 6.2 (2,810 Gm.) | Birth | + | .. | .. | + | + | + | .. | Bilateral otitis media, rales | ..... | Moderate | Slight | Rickets |
| W. O'C. | 9 | M | 4 mo.<br>20 days | 13.9 (6,310 Gm.) | Birth<br>2.5 mo. | ..<br>+ | ..<br>.. | +<br>.. | ..<br>.. | ..<br>+ | ..<br>.. | ..<br>.. | Dulness over base of right lung | Blood; negative; throat: Staph. aureus | Moderate | Moderate | |
| C. M. S. | 10 | F | 5 mo. | .... | Late | .. | .. | .. | .. | + | + | .. | Rales, nuchal rigidity, positive Kernig sign | Blood, spinal fluid: H. influenzae; bronchoscopic mucus: Staph. aureus | Moderate | Slight | Glomerulonephritis |
| **Group C** | | | | | | | | | | | | | | | | | |
| B. W. | 11 | F | 70 days | 10 (4,540 Gm.) | 7 wk.<br>4 mo. | ..<br>+ | ..<br>.. | ..<br>.. | ..<br>+ | +<br>.. | ..<br>.. | ..<br>.. | Bilateral otitis media, rales, marasmus, flat buttocks | Bronchoscopic mucus: Staph. aureus | Severe | Severe | |
| J. A. F. | 12 | M | 8 mo. | 9.5 (4,310 Gm.) | Birth<br>19 wk. | ..<br>.. | ..<br>.. | +<br>.. | ..<br>.. | ..<br>+ | ..<br>.. | ..<br>.. | Abdominal distention, rales | ..... | Moderate | Moderate | |
| T. B. | 13 | M | 9 mo. | 15.2 (6,900 Gm.) | Birth<br>Late | ..<br>.. | +<br>.. | +<br>.. | ..<br>+ | +<br>.. | ..<br>.. | ..<br>.. | Inguinal hernia on left side, rales | Throat: Staph. aureus | Moderate | Moderate | |
| E. R. | 14 | F | 10 mo.<br>23 days | 12.5 (5,675 Gm.) | Birth<br>Late | +<br>.. | ..<br>.. | ..<br>.. | ..<br>.. | ..<br>+ | ..<br>+ | ..<br>+ | Cyanosis, rales, palpable liver and spleen | ..... | Moderate | Moderate | |
| M. E. M. | 15 | F | 1 yr. 3 mo. | 18 (8,160 Gm.) | Late | + | .. | .. | + | + | + | .. | Underdevelopment, rales, anasarca | Blood: Staph. aureus; throat: Staph. aureus | Moderate | Moderate | Granuloma of lung; acid-fast bacteria absent |
| M. A. R. | 16 | F | 9 yr. 10 mo. | .... | Late | .. | .. | .. | + | + | + | + | Underdevelopment, rales, cyanosis | ..... | Moderate | Moderate | |
| P. S. | 17 | F | 10 yr. 1 mo. | .... | Late | + | .. | .. | .. | + | .. | .. | Dulness over base of left lung, rales, abdominal pain | Sputum: Str. viridans and Staph. aureus | Moderate | Slight | Infarct of myocardium |
| P. McG. | 18 | M | 3 yr. | .... | 8 mo. | + | + | + | + | + | + | + | Patchy dulness of lungs, cyanosis, abdominal distention | Bronchoscopic mucus: H. influenzae; blood; negative | Severe | Severe | Acute interstitial nephritis |

toward the periphery. There was clubbing of the fingers. The reaction to the Mantoux test with tuberculin in a concentration of 1:500 was negative. The temperature ranged between normal and 103 F.

Laboratory data were as follows: Three stool specimens had no foul odor but excessive amounts of fat. The average value by dry weight was total fat 36 per cent, of which "split" fat constituted 1.9 per cent and neutral fat, 34 per cent. The duodenal contents contained no trypsin. The dextrose tolerance curve was flat. Cultures of material from the postpharyngeal region showed great numbers of Staphylococcus aureus. The urine and blood were normal. The administration of pancreatin in doses of 1.5 Gm. three times a day gave little improvement. The child died on Aug. 17, 1943, and permission for autopsy was not obtained.

The 18 proved cases were gleaned from 640 cases in which necropsies were performed at the Children's Hospital in Pittsburgh from Jan. 1, 1936 to June 1, 1943 and represent 2.8 per cent of the total number. In the hospital during this same period celiac disease was diagnosed in 15 patients, and treatment was given. One of these patients, J. A. F. (case 12), as revealed at necropsy, died of cystic fibrosis of the pancreas. No instances of cystic fibrosis of the pancreas were found in the autopsies performed during the ten years previous to 1936. The incidence reported at the Children's Hospital in Pittsburgh (1936 to June 1943) is higher than that reported by Blackfan and May,[4] who found cystic fibrosis of the pancreas in 35 of 2,800 necropsies at the Children's Hospital in Boston. Farber[3] cites the occurrence of this disease in 52 of 1,089 patients who came to autopsy at the Children's Hospital in Boston during 1937 to 1942 inclusive, an incidence of 4.8 per cent. In 1942 necropsies were performed on 198 persons, of whom 16, or 8 per cent, had pancreatic fibrosis. These figures indicate a significant increase in cystic fibrosis of the pancreas during recent years.

In the table the patients have been grouped according to Andersen's classification of the types of cystic fibrosis of the pancreas. Only 1 of our patients falls into the A group, in which the condition is characterized by atretic lesions of the small intestine or pancreatic duct and early death. This child had an atresia of the circular musculature of the intestine with stenosis at a point 40 inches (100 cm.) below the origin of the jejunum. Death was due to peritonitis following dilatation and perforation of the intestine above this point. Patient C. S. (case 2, group B), who died at 21 days of age, had partial obstruction of the hepatic duct with jaundice. The remainder of our patients are equally distributed in groups B and C.

The disease was diagnosed for only 3 of our patients, W. O'C. (case 9), B. W. (case 11) and M. A. R. (case 16), during life, largely because of lack of presenting symptoms. This experience is similar to that reported from other hospitals. Cystic fibrosis of the pancreas is now well established as a definite disease and should be considered in the differential diagnosis and treatment of children who present maldigestion of fat and in whom staphylococcic infections of the respiratory tract refractory to therapy develop early in life. An analysis of the roentgenograms of our patients suggests that the bilateral and symmetric distribution of shadows in the lungs with enhanced hilar clouding in chronic pulmonary infections may be indicative of this condition, as premised by Attwood and Sargent.[5] The appearance of the stools and their increased fat content, especially in the form of neutral fats, is of limited value because such observations are also commensurate with the diagnosis of celiac disease. Apparently the most pathognomonic feature of cystic fibrosis of the pancreas is absence of pancreatic enzymes from the duodenal contents, the most reliable evidence of which is a negative reaction in tests for trypsin.[6] The associated lesions are the result of the deficient digestion and absorption of fat in which vitamin A is dissolved and retained which is caused by the diminution in pancreatic secretion. Both substances are lost to the body through increased elimination of fat. Staph. aureus is a common inhabitant of the mucosa of the upper respiratory tract of the normal person, and in event of a lowered resistance it would be the first organism to profit.

No definite causes for the pancreatic changes have been found to date, but tentative theories have been proposed. Although definite obstruction of the pancreatic ducts or the small intestine would seem to offer tangible evidence of causation, it is probable, from evidence offered in the

4. Blackfan, K., and May, C.: Inspissation of Secretion, Dilatation of the Ducts and Acini, Atrophy and Fibrosis of the Pancreas in Infants, J. Pediat. **13**: 627-634 (Nov.) 1938.

5. Attwood, C. J., and Sargent, W. H.: Cystic Fibrosis of Pancreas with Observations on Roentgen Appearance of Associated Pulmonary Lesions, Radiology **39**:417-425 (Oct.) 1942.

6. Andersen, D. H.: Cystic Fibrosis, Vitamin A Deficiency and Bronchiectasis, J. Pediat. **15**:763-771 (Dec.) 1939.

recent review by Kaufmann and Chamberlin,[7] that the pancreatic lesions precede the atresia and are the cause and not the result of these rare abnormalities. The theory of fetal inflammation fails because of the absence of inflammatory cells and the presence of normal islet tissue. Congenital syphilis may produce a pathologic picture in the pancreas approximating cystic fibrosis, but other characteristics of this disease are absent. Congenital malformations of the acini or alterations in the pancreatic secretions have not been demonstrated. No direct evidence of an alteration of the acinar secretion to produce an inspissating material has been adduced. The fact observed by Thomas and Schlutz,[8] that there are pathologic changes in accessory pancreatic tissue in the jejunum which are identical with the changes in the main organ, argues that intrinsic biochemical alterations in the acinar epithelium are probably a fundamental etiologic factor. Recently we observed such changes after sulfathiazole therapy for four weeks in a child of 6 months. In addition to widespread focal necrosis in the liver, spleen, lymph nodes, lungs, kidneys and small intestine, acinar degeneration and necrosis in conjunction with early cystic fibrosis occurred in the pancreas.

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7. Kaufmann, W., and Chamberlin, D. B.: Congenital Atresia of Pancreatic Duct System as a Cause of Meconium Ileus, Am. J. Dis. Child. **66**:55-67 (July) 1943.

8. Thomas, J., and Schlutz, F. W.: Pancreatic Steatorrhea, Am. J. Dis. Child. **56**:336-343 (Aug.) 1938.

# FATAL EFFECTS OF PROLONGED COMPLETE CURARIZATION

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Of the convulsive disorders none is more severe than tetanus. Its victim is conscious (except in the terminal stages) and suffers excruciating pain from generalized spasms so violent as frequently to cause compression fractures of the vertebrae. When these convulsions involve the respiratory muscles, as they commonly do, sudden death from acute asphyxia may ensue. Although the ultimate cause of death in tetanus may be organic changes in the brain [1] or inhibition of some vital enzymatic action,[2] the immediate cause appears clinically to be either respiratory spasms or a terminal aspiration bronchopneumonia.

The active treatment of tetanus is twofold and consists specifically in the injection of tetanus antitoxin to neutralize the unbound circulating toxin and symptomatically in the administration of sedatives (such as solution of tribromoethanol or one of the barbiturates) or anticonvulsants (magnesium sulfate, for example) to control the spasms. Unfortunately the administration of tetanus antitoxin does not immediately retard the aggravation of symptoms, which usually increase in severity for several days. Thus patients entering the hospital with relatively few and mild spasms may become, in the course of one to four days, subject to severe convulsive seizures, in spite of the fact that they received adequate doses of antitoxin on admission.

The dose of a sedative necessary to control the convulsive symptoms of severe tetanus during this critical period may be so great as to constitute a hazard of central suppression of respiration with resulting asphyxia or fatal bronchopneumonia.

Since curare is generally thought to exert its paralyzing action solely at the myoneural junction and to be without other important pharmacologic activity, it seems logical to assume that it might be possible to control all of the convulsive symptoms of tetanus with this drug. If respiration should be maintained by placing the curarized patient in a mechanical respirator, it would seem theoretically possible to tide the patient over for several days, until the convulsive symptoms began to subside. The feasibility of such a procedure was suggested by Claude Bernard,[3] who stated that with artificial respiration one should be able to maintain life for a prolonged period in completely curarized animals.

Since 1859 [4] attempts have been made to treat the convulsive phase of tetanus with curare. Although there have been many reports of favorable results in isolated cases,[5] therapy for tetanus with curare has remained in the experimental stage chiefly because of the uncertain supply and the variable potency of the drug. Recently a supply of standardized curare has become available,[6] and numerous reports have been published on its safety and efficacy in preventing violent convulsions due to the treatment with metrazol [7] of persons with psychoses. To such patients curare

This study was aided by a grant from the Kunstadter Fund for Pediatric Research.

From Sarah Morris Hospital for Children and the Department of Metabolism and Endocrinology of Michael Reese Hospital.

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2. Firor, W. M.: Internat. Abstr. Surg. **75**:185, 1942.

3. Bernard, C.: Leçons sur les effects des substances toxiques et medicamenteuses, Paris, J. B. Baillière et fils, 1883, lesson 21, p. 305.

4. Wells, T. S.: Proc. Med.-Chir. Soc., London **3**:142, 1859.

5. (*a*) Hoffman, F. A.: Berl. klin. Wchnschr. **16**: 637, 1879. (*b*) Chesterfield: Lancet **2**:831, 1904; cited by Collins, E.: ibid. **1**:990, 1905. (*c*) West, R.: Brit. M. J. **2**:1173, 1934. (*d*) Cole, L.: Quart. J. Med. **4**:295, 1935. (*e*) Mitchell, J. S.: Lancet **2**:475, 1934.

6. In 1934 Mr. Richard C. Gill returned from South America with the first large supply of authenticated crude curare. It was from this supply that E. R. Squibb & Sons extracted and standardized substantial quantities of curare, which is now available as intocostrin.

7. (*a*) Bennett, A. E.: Preventing Traumatic Complications in Convulsive Shock Therapy by Curare, J. A. M. A. **114**:322 (Jan. 27) 1940; Am. J. Psychiat. **97**:1040, 1941. (*b*) Gray, R. W.; Spradling, F. L., and Fechner, A. H.: Psychiatric Quart. **15**:159, 1941. (*c*) Shelton, P.: J. Missouri M. A. **38**:120, 1941. (*d*) Harris, M. M.; Pacella, B. L., and Horwitz, W. A.: Psychiatric Quart. **15**:537, 1941. (*e*) Bennett, R. J.: Northwest Med. **40**:280, 1941. (*f*) Ziferstein, I.: J. Iowa M. Soc. **31**:531, 1941. (*g*) Goldman, D., and Baber, E. A.: Am. J. M. Sc. **203**:354, 1942. (*h*) Cleckly, H. M.; Hamilton, W. P.; Woodbury, R. A., and Volpitto, P. P.: South. M. J. **35**:375, 1942. (*i*) Kolb, L., and Vogel, V. H.: Am. J. Psychiat. **99**:90, 1942. (*j*) Charlton, G. E.; Brinegar, W. C., and

*(Footnotes continued on next page)*

is administered over relatively short periods and in doses insufficient to cause respiratory paralysis. For the treatment of tetanus it might be necessary to maintain complete curarization for two to four days. We therefore decided to test the feasibility of such prolonged complete curarization on dogs before attempting it in human beings with severe tetanus.

## PRELIMINARY EXPERIMENTS

Eight preliminary experiments were done to establish the conditions for prolonged curarization (table 1).

TABLE 1.—*Curarization and Artificial Respiration Without Administration of Other Drugs*

| Dog No. | Curare, Cc. | Prep-aration * | Survival Time | Probable Cause of Death | Tracheal Cannula |
|---|---|---|---|---|---|
| 1 | 3.8 | I | 1 hr. 28 min. | Asphyxia | Not used |
| 2 | 7.0 | I | 3 hr. 45 min. | Asphyxia | Not used |
| 3 | 1.25 | I | 10 min. | Asphyxia | Not used |
| 4 | 1.5 | I | 11 min. | Asphyxia | Not used |
| 5 | 2.2 | I | 1 hr. 23 min. | Killed | Used |
| 6 | 3.0 | I | | | |
| | 12.9 | T | 7 hr. 10 min. | Killed | Used |
| 7 | 15.0 | T | 1 hr. | Asphyxia | Used but removed 8 min. before death |
| 8 | 14.0 | T | 2 hr. 33 min. | Killed | Used |

* I indicates that intocostrin was used and T that d-tubocurarine dimethyl ether iodide was used.

*Method.*—A normal dog was anesthetized by the intravenous administration of pentothal sodium, a vein in the leg was cannulated and tracheal intubation was performed. After the dog emerged from the anesthesia, curare or d-tubocurarine dimethyl ether iodide [8] was injected intravenously until all muscular movement, including respiratory movement, stopped. A continuous intravenous infusion of an isotonic solution of sodium chloride was given to keep the animal in fluid balance. In some animals the blood pressure was observed by the use of a mercury manometer connected through a tube containing sodium citrate solution with the carotid artery. Respiration was maintained with an Emerson infant respirator [9] equipped with a suction aspirator which operated during expiration only. The respiratory rate and amplitude were adjusted to the needs of the dogs, as estimated by the carbon dioxide tension of the exhaled air.

For estimation of the carbon dioxide tension an apparatus based on the principle formulated by Higgins and Marriott [10] was used. The exhaled air was aspirated through a long, narrow glass tube attached to the tracheal cannula and was bubbled through a solution of 0.002 per cent phenolsulfonphthalein (phenol red) in hundredth-normal sodium hydroxide. The carbon dioxide tension of the air bubbling through the solution determines its $p_H$ and thus the color of the phenolsulfonphthalein; this color is compared with those of standard solutions of known carbon dioxide tension (Peters and Van Slyke [11]). The respirator was adjusted to keep the carbon dioxide tension at the optimal level of 30 to 40 mm. of mercury.

*Observations.*—A dose of intocostrin or of d-tuberocurarine dimethyl ether iodide corresponding to 2 to 2.5 mg. of standard curare per kilogram given intravenously caused complete paralysis for about thirty minutes. Repeated doses of curare sufficient to maintain complete curarization were administered at intervals of thirty to sixty minutes. The musculature of the head and limbs was paralyzed first; the intercostal muscles and the diaphragm, last. Animals in which asphyxia occurred frequently exhibited jerky respiratory movements or even generalized convulsions.

It was found advisable to retain the tracheal tube in situ during the whole period of complete curarization. Otherwise asphyxia occurred as a result of obstruction of the airway by the falling back of the tongue or, more seriously, by the valvelike action of the relaxed epiglottis, which fell over the glottis and prevented the ingress of air, even when the tongue was forcibly drawn forward. Although it was possible to overcome this tendency by pulling the epiglottis forward by means of a suture, the procedure often caused severe edema and the suture tended to pull out easily. Because all of our animals were "debarked" by excision of the vocal cords, we were unable to observe the effect of curarization on these structures.

## EXPERIMENTS WITH PROLONGED CURARIZATION

In the second series of experiments it was attempted to keep curarized dogs alive for several days. To maintain sufficient caloric intake, a 5 per cent solution of dextrose in water was given to the animals by continuous intravenous drip (about 0.25 Gm. of dextrose per kilogram per hour). In the first 3 experiments the dogs were kept completely paralyzed until death; in the

Holloway, O. R.: Curare and Metrazol Therapy of Psychoses: Report of Fatal Case, Arch. Neurol. & Psychiat. **48**:267 (Aug.) 1942. (*k*) Woolley, L. F.; Jarvis, J. R., and Ingalls, G. S.: J. Nerv. & Ment. Dis. **96**:680, 1942. (*l*) Jones, G. L., and Pleasants, E. N.: Dis. Nerv. System **4**:17, 1943. (*m*) Cash, P. T., and Hoekstra, C. S.: Psychiatric Quart. **17**:20, 1943. (*n*) Hoekstra, C. S., and Lowenbach, H.: North Carolina M. J. **4**:123, 1943.

8. (*a*) King, H.: Nature, London **135**:469, 1935; J. Chem. Soc. London, October 1935, pt. 2, p. 1381; Chem. Abstr. **29**:7337, 1935. (*b*) The intocostrin and d-tubocurarine dimethyl ether iodide were supplied by Dr. H. S. Newcomer, of E. R. Squibb & Sons, New York.

9. Loaned by the J. H. Emerson Co., Cambridge, Mass.

10. (*a*) Higgins, H., and Marriott, W. M.: J. Am. Chem. Soc. **39**:68, 1917. (*b*) Marriott, W. M.: The Determination of Alveolar Carbon Dioxid Tension by a Simple Method, J. A. M. A. **66**:1594 (May 20) 1916.

11. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry: II. Methods, Baltimore, Williams & Wilkins Company, 1933, p. 151.

remainder it was attempted to keep the dogs only partially paralyzed, to the extent that some spontaneous respiration was still possible.

The results of the second series of experiments are recorded in table 2. The first 2 dogs received intocostrin. The first died because of an obstructed airway. Cardiac arrhythmia and bradycardia developed in the second dog after about three hours of continuous curarization. Finally tachycardia appeared, and the dog died after about fifteen hours of curarization. At necropsy the heart was found to be greatly dilated and a moderate congestion of the viscera was observed. It was thought that possibly the inhibitory effect of intocostrin on cholinesterase [12] had resulted in an accumulation of acetylcholine, which had induced cardiovascular changes that were ultimately fatal. For that reason d-tubocurarine dimethyl ether iodide, which, it is claimed, does not inhibit cholinesterase, was used in all of the subsequent experiments. Dog 3 (table 2) was kept completely paralyzed. In this animal also arrhythmia appeared after a period of bradycardia. This anmial died after eight hours and twenty minutes of continuous complete curarization, and at necropsy its heart was slightly distended.

It appeared that curare had some cardiotoxic action that became evident only after the animal had received enough curare or else had been under the influence of curare for a long enough period. In subsequent experiments, therefore, it was attempted to allow intermittent periods of freedom from the influence of curare, so as to avoid a cumulative effect of the toxic agent. During these periods the paralysis was only sufficient to keep the animal quiet, and some degree of spontaneous respiration was present. It was found, however, that the use of sufficient curare to keep the dog quiet necessitated the use of artificial respiration for at least 50 per cent, and in some animals for the whole, of the duration of the experiment in order to keep the animal properly oxygenated.

TABLE 2.—*Effects of Other Drugs on Animals Receiving Curare*

| Dog No. | Total Amount of Curare, Cc. | Preparation * | Survival Time | Artificial Respiration | Pulse | Other Drugs Administered | Postmortem Conditions |
|---|---|---|---|---|---|---|---|
| 1 | 9.0 | I | 2 hr. 50 min. | Continuous | Regular | ..... | Obstructed airway |
| 2 | 30.0 | I | 14 hr. 55 min. | Continuous | Arrhythmia | Neostigmine; ephedrine; 1,800 cc. 5% dextrose | Dilated heart; visceral edema |
| 3 | 17.0 | T | 8 hr. 20 min. | Continuous | Arrhythmia | 700 cc. 5% dextrose | Dilated heart; visceral edema |
| 4 | 32.6 | T | 45 hr. 13 min. | Intermittent 27 hr. 39 min. | Arrhythmia, bradycardia | 2,730 cc. 5% dextrose | Dilated heart; visceral edema |
| 5 | 28.4 | T | 27 hr. 50 min. | Intermittent 15 hr. 34 min. | Arrhythmia | 1,525 cc. 5% dextrose | Dilated heart; visceral edema |
| 6 | 2.5 | T | 2 hr. 55 min. | Intermittent 2 hr. 40 min. | Tachycardia, bradycardia | 330 cc 5% dextrose | Dilated heart |
| 7 | 3.0 | T | 1 hr. 10 min. | Intermittent 1 hr. 5 min. | Tachycardia | 150 cc. 5% dextrose; atropine sulfate † 1 mg./Kg. | Normal heart; dilated stomach |
| 8 | 2.0 | T | 26 min. | Continuous | Regular | Atropine sulfate,† 1 mg./Kg. | Organs looked normal |
| 9 | 2.0 | T | 5 min. | Continuous | Regular | Atropine sulfate,† 1 mg./Kg. | Organs looked normal |
| 10 | 4.5 | T | 5 hr. 57 min. | Intermittent 2 hr. 37 min. | Fast then irregular and slow | Atropine sulfate, 0.01 mg./Kg.; 350 cc. 5% dextrose | Dilated heart |
| 11 | 8.5 | T | 9 hr. 5 min. | Intermittent 6 hr. 23 min. | Regular and rapid | 5 mg. pilocarpine hydrochloride; 750 cc. 5% dextrose | Dilated heart (hyperpyrexia); visceral hyperemia |
| 12 | 4.0 | T | 3 hr. 25 min. | Continuous | Regular | Ergotamine tartrate; 270 cc. 5% dextrose | Dilated heart |

* I indicates administration of intocostrin; T, of d-tubocurarine dimethyl ether iodide.
† Atropine given one hour before curare.

Under these conditions 2 dogs (4 and 5 in table 2) lived for forty-five hours and thirteen minutes and for twenty-seven hours and fifty minutes respectively; a third (6, table 2) lived only two hours and fifty-five minutes. At necropsy all of these dogs showed the same cardiac dilatation and visceral congestion noted in the animals used in the preceding experiments. Because bradycardia was noticed frequently, it was considered possible that acetylcholine was the cardiotoxic agent. It was therefore attempted to keep the next 4 curarized dogs alive by continuous atropinization. Two dogs (8 and 9 in table 2) in such experiments lived less than an hour after both drugs were injected intravenously; one of these animals (9, table 2) died within five min-

12. McIntyre, A. R., and King, R. E.: Science **97**: 69, 1943.

utes. No cardiac dilatation was found to explain the deaths. A fourth dog (10, table 2) given a much smaller dose of atropine died, after a terminal period of cardiac arrhythmia, five hours and fifty-seven minutes after curarization was begun. The heart of this animal was greatly dilated. For all of these atropinized animals the dose of curare necessary to maintain paralysis was much less than for animals not given atropine.

Curare is known to be antagonistic to the cardioinhibitory action of pilocarpine.[13] In the hope of nullifying the cardiotoxic action of curare, the next curarized dog (11, table 2) was given 1 mg. of pilocarpine hydrochloride subcutaneously at half hour intervals. This dog had a progressive rise in temperature and died after nine hours and five minutes of curarization. The heart was dilated, and there was an intense congestion of the abdominal blood vessels. Ergotamine tartrate was the other sympathomimetic agent used in conjunction with curare. In the dog receiving this drug (12, in table 2) cardiac arrhythmia appeared, and the animal died with a dilated heart three hours and twenty-five minutes after curarization was begun.

The possibility was considered that curare, by its paralyzing effect on the skeletal musculature, was indirectly responsible for an accumulation of serum potassium, which exerted the toxic action on the heart. Accordingly a dog (not included in table 2) was kept completely curarized, by an intramuscular injection of d-tubocurarine dimethyl ether iodide, and the potassium content of the serum and the hematocrit reading were followed, as shown in table 3.

TABLE 3.—*Effect of Curare on the Potassium Content of the Serum*

| Duration of Curarization | Hematocrit Reading | Serum Potassium, Mg./100 Cc. |
|---|---|---|
| Control | 37 | 20.2 |
| 2 hours | 37 | 20.0 |
| 4 hours | 42 | 15.5 |
| 6 hours | 44 | 21.4 |

It is evident that the potassium content of the blood was unaffected by six hours of curarization and that the action of accumulated serum potassium was, therefore, not the mechanism of the cardiotoxic action.

## COMMENT

Curare is known to paralyze autonomic ganglions and to stop the heart in frogs, molluscs and arthropods. In mammals, however, curare was thought to have little effect on the heart until McIntyre[14] found that it caused a fall in blood pressure and an inversion of the T wave in the electrocardiogram. Neither intocostrin nor d-tubocurarine dimethyl ether iodide affected the blood pressure in our experiments on acute intoxication.

At necropsy in our animals it was found consistently that the heart, especially the right side of the heart, was dilated and that the liver and kidneys were congested. No other gross lesions were noted. The only dogs that did not have dilated hearts were those that had been atropinized before symptoms of impaired cardiac function appeared. These animals lived less than seventy minutes, except for the 1 dog that received extremely small doses of atropine; it lived for almost six hours and had severe cardiac dilatation.

Rapid death after curarization occurred consistently in the atropinized dogs listed in table 2. In 2 curarized dogs not included in the tables the injection of a physiologic dose of atropine resulted in immediate death. It was noted in the atropinized dogs that lived long enough that less curare was needed and that the effect of curare lasted longer than in animals not receiving atropine. These results are in keeping with those reported by Rosenblueth and his co-workers,[15] who found that atropine delayed decurarization by neostigmine and also with those reported by J. C. Burke,[16] who also found that rapid death followed intravenous injections of atropine in 2 curarized dogs. Burke suggested that the deaths might be caused by ventricular fibrillation, owing to the removal of vagal inhibition by atropine.

It was thought that an accumulation of serum potassium might result from prolonged and profound muscular paralysis. The excess potassium might be the cardiotoxic agent. No significant change in total serum potassium was found, however, in a dog kept completely curarized for six hours. This dog, also, showed a dilated heart at necropsy.

At no time did we encounter an appreciable amount of bronchial or tracheal secretions except when pilocarpine was used or when the dogs were asphyxiated.

Our experiments give no clear indication as to the exact cause of death in prolonged curarization. They do, however, point to the heart as the organ principally affected. Irregularity and slowing of the pulse were found regularly, and on autopsy the heart was seen to be dilated.

13. Hamet, R.: Compt. rend. Soc. de biol. **115**:602, 1934.

14. McIntyre, A. R.: Curare, Sigma XI Lecture, University of Illinois, April 14, 1943.

15. Rosenblueth, A.; Lindsley, D. B., and Morison, R. S.: Am. J. Physiol. **115**:53, 1936.

16. Burke, J. C.: Personal communication to the authors.

Whether the cardiac failure was due to the prolonged direct effect of curare on the heart or to an indirect effect through an influence on circulation or on the vasomotor centers is impossible to conclude from the present data. It is clear, however, that continuous administration of curare not only affects the neuromuscular junctions of the skeletal muscles but exerts an action on internal organs and/or the central nervous system.

The precise mechanism of the action of curare is at present unknown. The recent work of McIntyre [14] indicates that curare and its derivatives may act directly on muscle by combining with and thus immobilizing the effector substance in muscle which acetylcholine normally activates, that is, curare acts as an inhibitor of the acetylcholine—muscle effector system. This concept, if substantiated more firmly, would point to the probable action of curare on all or most processes activated by acetylcholine, such as activity of the internal organs and neural transmission. A detailed study of the action of curare on the known enzymatic systems of various vital organs is therefore necessary. Only such knowledge can provide a firm basis for the clinical application of the drug.

In view of our results we must warn against the use of curare for more than short periods until the cause of the toxic action demonstrated by our experiments [17] has been found and methods have been developed to counteract it. The lethal effect of prolonged curarization has been, to our knowledge, hitherto undescribed.

## CONCLUSION

Prolonged curarization has a lethal effect in animals in spite of artificial maintenance of respiration. This effect, hitherto not described, precludes the clinical use of curare for prolonged periods, as would be necessary in the treatment of tetanus.

Atropine hastens the lethal effect of curare. The administration of atropine to curarized patients should therefore be avoided.

Dr. S. Soskin and Dr. R. Levine, of the Department of Metabolism, aided in the technical aspects of this work.

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17. Mr. J. C. Burke of the E. R. Squibb Laboratory, New Brunswick, N. J., has repeated our experiment in 8 dogs, with identical results.

# STUDIES ON THE CONTROL OF ACUTE INFECTIONS OF THE RESPIRATORY TRACT

## III. RESULTS OF SULFADIAZINE THERAPY FROM MAY 3, 1942 TO MAY 2, 1943

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The influence of sulfadiazine on the course of the more common infections of the respiratory tract has been studied in this laboratory since 1941.[1] It will be recalled that originally treatment with sulfadiazine was started at the onset of symptoms of respiratory illness in order to establish whether bacteriostatic action on susceptible organisms primarily or secondarily involved might, in turn, affect the severity of the disease. While some of the patients observed during 1941 and 1942 were aided by the early use of sulfadiazine, others apparently were not benefited. The ameliorating effects observed were most striking in January and February 1942, during an outbreak of severe illnesses which were characterized by severe toxemia and high incidence of acute bronchitis and of pneumonia due to Pneumococcus type I. Shortly afterward sulfadiazine was used without measurable effect in an outbreak of relatively mild, uncomplicated infections presumably of viral origin.[1a] There were also sporadic illnesses, throughout the year, which were clearly unmodified by the use of the drug. There were no serious ill effects referable to the drug, although the possibilities of toxic reactions, "sensitization" of the population treated and transformations of bacterial strains resistant to the action of the drug were constantly kept in mind. The encouraging results at this time, as well as the need for additional clinical data on the value and limitations of the treatment, led to a continuation of the study during 1942 and 1943.

The work was carried out at Letchworth Village, an institution of the state of New York for feebleminded patients, among children highly susceptible to infections of the respiratory tract and to secondary bacterial complications. The children observed varied in age from 2 to 15 years, the average age being 8.1 years. They lived in two cottages, a group of about 130 girls in cottage Y and an approximately equal number of boys in cottage Iota. New admissions to each cottage replaced withdrawals at the rate of about 1 per week. The duration of residence varied considerably, ranging from a few months to several years and averaging two and three-tenths years. About 90 per cent of the patients were white children; 10 per cent, Negroes. Their average weight was 42 pounds (19 Kg.). Mongoloid features characterized about 20 per cent of the children.

The children were assigned to the control or to the sulfadiazine-treated ("treated") group in alternate order of admission to each cottage. The groups were comparable with regard to age, weight, frequency of mongolism and past incidence of pneumonia and other acute infections of the respiratory tract.

The children in the two groups were managed alike, except for the use of sulfadiazine in the treated group at the onset of clinical infections of the respiratory tract. During late 1941 and early 1942,[1b] when the drug was usually administered for three or four days, there were frequent secondary rises in temperature shortly after withdrawal of the drug. In an effort to diminish the frequency of such rises in temperature, during the present study the drug was prescribed for seven days as follows: 2.0 to 2.5 Gm. on the first day of illness; 2 Gm. daily for the next three days, and 1 Gm. daily for the last three days. The daily dose was given in equally divided amounts, at 8, 12, 4 and 8 o'clock. The average level of free sulfadiazine in the blood varied usually from 4 to 10 mg. per hundred cubic centimeters when a daily maintenance dose of 2 Gm. was given.

From the Division of Infectious Diseases, the Public Health Research Institute of the City of New York.

Aided by a grant from the Metropolitan Life Insurance Company on the recommendation of the Influenza-Pneumonia Commission.

1. (*a*) Siegel, M.: Studies on the Control of Acute Respiratory Infections: I. Preliminary Report on the Oral Administration of Sulfadiazine at the Onset of Acute Respiratory Illnesses, J. A. M. A. **119**:783 (July 4) 1942; (*b*) Studies on the Control of Acute Infections of the Respiratory Tract: II. Oral Administration of Sulfadiazine at the Onset of Acute Respiratory Illnesses, Am. J. Dis. Child. **66**:114 (Aug.) 1943. (*c*) Siegel, M., and Julianelle, L. A.: The Epidemiology of Acute Respiratory Infections Conditioned by Sulfonamides: I. General Clinical Considerations, to be published.

## RESULTS

The period of observation covered in the present report lasted from May 3, 1942 to May 2, 1943 in cottage Iota and from Oct. 4, 1942 to May 2, 1943 in cottage Y. During these periods, 250 acute infections of the respiratory tract were studied in 130 patients. They were distributed by cottage and group as follows:

| Cottage | Period of Observation | No. of Infections: Treated Group | No. of Infections: Control Group | No. of Patients: Treated Group | No. of Patients: Control Group |
|---|---|---|---|---|---|
| Iota | 5/3/42 to 5/2/43 | 93 | 55 | 40 | 32 |
| Y | 10/4/42 to 5/2/43 | 53 | 49 | 29 | 29 |
| Total | | 146 | 104 | 69 | 61 |

Most of the illnesses were mild uncomplicated infections of the upper respiratory tract, and they were considerably milder than those observed in the preceding studies.[1a,b] There were no outbreaks of severe infections, such as had occurred regularly each year in the past, and the incidence of typical pneumonia and secondary bacterial complications was the lowest ever recorded at the institution.[1c] Concurrent bacteriologic studies of the nasopharyngeal flora made during this period have been presented in separate reports.[2]

Excluded from the study were 22 infections (15 per cent of the total) in patients in the treated group which had not been treated with sulfadiazine for various reasons and 11 infections (11 per cent of the total) in patients in the control group which had been treated contrary to plan. The former were usually mild infections, while the latter appeared to be severe at the onset and to require immediate drug therapy. The exclusion of these illnesses from the study eliminated some of the more severe infections in the control group and some of the less severe illnesses in the treated group. This type of selection necessarily favors the controls, but it is nevertheless unavoidable, since the therapeutic value of sulfadiazine against such infections renders censurable its withholdance.

The clinical results obtained have been studied from the standpoint of (1) the number of colds per person and (2) the maximum temperature on the first day of illness. The following objective data were noted: average duration of fever (rectal temperature above 100 F.) after the first day's treatment in bed; rise in temperature in the early stages of illness following the first day's treatment (primary rise); subsequent rise in temperature (secondary rise), and number of illnesses requiring hospitalization. Since the data from cottages Y and Iota were comparable, they have been combined, for the sake of brevity, in the presentation that follows.

A summary of the results obtained in the treated and in the control group is given in table 1. The number of infections per person was somewhat greater among the treated patients than among the controls. However, the two groups were comparable with regard to the temperature level on the first day of illness. This was 103 F. or more in 23 per cent of the attacks, 101 to 102.9 F. in about 40 per cent and less than 101 F. in the remainder.

The average duration of fever after the first day's treatment was one and one-tenth days for the treated patients and two and three-tenths

TABLE 1.—*Comparison of Results in Treated and in Control Patients with Acute Infections of the Respiratory Tract During 1942-1943*

| Classification of Illnesses | Number of Infections: Treated | Number of Infections: Controls | Average Duration of Fever after First Day's Treatment: Treated | Average Duration of Fever after First Day's Treatment: Controls | Frequency* of Primary Rise in Temperature: Treated | Frequency* of Primary Rise in Temperature: Controls | Frequency* of Secondary Rise in Temperature: Treated | Frequency* of Secondary Rise in Temperature: Controls | Frequency* of Hospitalization After First Day's Treatment: Treated | Frequency* of Hospitalization After First Day's Treatment: Controls |
|---|---|---|---|---|---|---|---|---|---|---|
| **A. Data Arranged According to the Number of Infections per Patient** | | | | | | | | | | |
| Number of Colds per Patient | | | | | | | | | | |
| 1 | 27 | 35 | 1.1 days | 2.2 days | 3.7 | 14.3 | 11.1 | 25.7 | 7.4 | 5.7 |
| 2 | 48 | 32 | 1.1 days | 1.6 days | 8.3 | 9.4 | 12.5 | 12.5 | 4.2 | 15.6 |
| 3 or more | 71 | 37 | 1.2 days | 3.0 days | 5.6 | 13.5 | 16.9 | 40.5 | 0.0 | 16.2 |
| Total | 146 | 104 | 1.1 days | 2.3 days | 6.1 | 12.5 | 14.4 | 26.9 | 2.7 | 12.5 |
| **B. Data Arranged According to the Maximum Temperature on the First Day of Illness** | | | | | | | | | | |
| Temperature on First Day | | | | | | | | | | |
| Less than 101 F. | 59 | 37 | 0.8 days | 1.4 days | 11.8 | 8.1 | 11.8 | 18.9 | 0.0 | 5.4 |
| 101 to 102 F. | 53 | 44 | 1.1 days | 2.3 days | 3.8 | 15.9 | 13.2 | 22.7 | 5.7 | 9.1 |
| 103 F. or more | 34 | 23 | 1.7 days | 2.7 days | 0.0 | 13.0 | 20.6 | 47.8 | 2.9 | 30.4 |
| Total | 146 | 104 | 1.1 days | 2.3 days | 6.1 | 12.5 | 14.4 | 26.9 | 2.7 | 12.5 |

* The frequency is stated on the basis of the percentage of infections in which the given condition occurred.

2. (*a*) Siegel.[1c] (*b*) Julianelle, L. A., and Siegel, M.: The Epidemiology of Acute Respiratory Infections Conditioned by Sulfonamides: II. Alteration in the Nasopharyngeal Flora Associated with Treatment, to be published; (*c*) III. Effect of Prolonged Administration of Sulfadiazine on Neisseriae, to be published; (*d*) IV. Effects on the Organism and Carrier of Diphtheria, to be published; (*e*) V. Trends in Pneumococcal Types Initiated by Drug Treatment, to be published.

days for the controls. It was consistently lower among the treated patients than among the controls, irrespective of the number of illnesses suffered by the person and of the temperature level at the onset (table 1).

A primary rise in temperature after the first day's treatment occurred in 9 infections (6 per cent) in treated patients and in 13 infections (13 per cent) in controls. The maximum temperature was reached by the second or third day of illness. In the infections in treated patients the primary rise occurred largely during subfebrile attacks, and the maximum temperature was not usually high. The temperature rose from between 99 and 100 F. to between 100 and 101 F. in 7 of the 9 infections. In 2 infections, however, the temperature rose from 102 F. to 104 F. on the second day of illness. In one the child had cervical adenitis secondary to an acute nasopharyngitis, and in the other he had an acute nasopharyngitis and bronchitis. The temperatures receded gradually to normal levels by the seventh and fifth days respectively. The

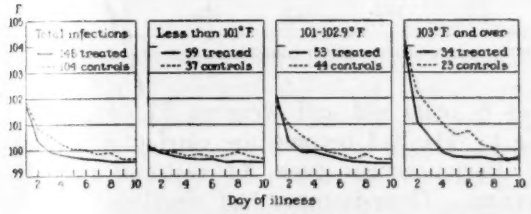


Chart 1.—Average daily temperatures in 250 infections of the respiratory tract observed during 1942-1943 in sulfadiazine-treated and untreated patients arranged according to the patient's maximum temperature on the first day of illness, as indicated by the figures in the top of each box.

temperatures in 6 of the other 7 infections in treated patients mentioned above dropped below 101 F. within twenty-four hours, and in the last the temperature remained at 101 F. for four days. In infections in the controls the temperature exhibited a primary rise about twice as often as in infections in the treated patients and reached fairly high levels; it rose from between 99 and 100 F. to between 101 and 105 F. in 3 cases, from between 101 and 102 F. to between 102 and 105 F. in 7 and from 103 F. to between 104 and 105 F. in 3. In no instance did typical pneumonia appear, although it was suspected in 4, in which the diagnosis eventually made was acute bronchitis and nasopharyngitis. All the other controls with primary rises in temperature had uncomplicated acute nasopharyngitis.

A secondary rise in temperature was observed in 21 infections (14 per cent) in the treated patients and in 28 infections (28 per cent) in the controls. Such a rise was not uncommon in either group, irrespective of the number of attacks suffered or the temperature level on the first day of illness. The secondary rise usually occurred on the third to the eighth day of illness. The maximum temperature reached was slightly lower in infections in the treated patients than in infections in the controls; it was 100 to 101 F. in 16 infections in treated patients and 16 in controls, 102 to 103 F. in 4 infections in treated patients and 11 in controls, and 104 to 105 F. in 1 infection in a treated patient and 1 in a control. The elevated temperature lasted for a somewhat shorter time among the treated patients, receding within twenty-four hours in 11 infections in treated patients and 4 in controls, in one to two days in 4 infections in treated patients and 13 in controls, in three to five days in 5 infections in treated patients and 7 in controls and in six to ten days in 1 infection in a treated patient and 4 in controls.

Secondary pneumonia was suspected in 2 treated patients and 7 controls who were hospitalized. Only 1 of these, a control, was shown to have bronchopneumonia, while the others were considered as having acute bronchitis or acute nasopharyngitis. All other patients with secondary rises in temperature had acute nasopharyngitis. Purulent otitis media was not observed, while purulent nasal discharge and chronically infected tonsils were commonly seen in both control and treated patients.

Secondary rises in temperature in treated patients occurred during the course of sulfadiazine therapy in all but one child, whose temperature rose twenty-four hours after withdrawal of the drug. The causes of the febrile reactions were usually obscure, particularly in patients with chronic inflammatory processes. In some instances the possibility of a febrile reaction to the drug was considered.

Hospitalization after the first day's treatment in the cottage was required with 4 infections (3 per cent) in treated patients and 12 infections (12 per cent) in controls, all of whom were suspected of having pneumonia. The diagnosis was confirmed by roentgenograms for 2 patients only, both controls. One had lobar pneumonia of the right middle lobe, and the other had bronchopneumonia, as previously mentioned. The former had a temperature of 105 F. on the first day of illness and early signs of consolidation at the onset. In the latter the temperature fluctuated between 101 and 103 F. for the first six days of illness and pulmonary signs suggestive of bronchopneumonia were detectable early in the disease. All the others who were hospitalized had acute nasopharyngitis with or with-

out bronchitis and were usually returned to their cottages within a week.

The average daily temperatures in infections in control and in treated patients is graphically shown in chart 1. The illnesses are grouped according to the maximum temperature on the first day, and the average daily temperature is plotted along the ordinate. At all temperature levels the curve for the treated illnesses dropped sharply on the second day and reached normal limits by the third, while the curve for the controls showed a more gradual decline.

A comparison of the results presented in the foregoing paragraphs with those obtained during the preceding year (1941-1942), when the illnesses were in general more severe, is shown in table 2 and chart 2. The average duration of fever after the first day's treatment was the same in both years in infections in treated patients, while in infections in the controls it was appreciably lower during the current year. The frequency of primary and secondary rises in temperature and the number of illnesses requiring hospitalization were also almost the same in both years in infections in treated patients, while in infections in the controls the frequency of a primary rise in temperature and of illnesses requiring hospitalization was somewhat less during the current year. The average daily temperatures in infections in treated patients varied little from one year to the other (chart 2). On the other hand, the temperatures in infections in controls were usually lower in 1942-1943 than in the preceding year. The differences observed among the controls in both years reflect the differences in the severity of the illnesses encountered. It is interesting that in the treated patients, however, a more or less uniformly mild course was observed, irrespective of the difference in severity of the infections.

On the whole, the illnesses were milder in treated patients than in the controls, although the degree of difference between the two groups was smaller in 1942-1943 than in 1941-1942, a difference which may be explained by the lessened severity of infections prevalent during 1942-1943. In both years some of the illnesses became worse despite sulfadiazine therapy, and improvement was so delayed in others as to leave in doubt the value of sulfadiazine in these instances. The frequency of a secondary rise in temperature during 1942-1943 remained high, even though sulfadiazine was used for a somewhat longer period than before.

No deaths occurred during the current period of observation. However, in May 1943, shortly after the termination of the study, 2 patients died of scarlet fever, 1 in the control group, on the third day of illness, and the other in the treated group, on the twentieth day. The latter patient was a white boy, of mongoloid type, who was 6 years old and weighed 33 pounds (15 Kg.). He had become the carrier of a strain of Pneumococcus type XI resistant to sulfadiazine. Drug-fastness had developed in this organism in vivo, while sulfadiazine was being administered daily from December 1942 to March 1943; and the organism had spread to

TABLE 2.—*Comparison of Results Obtained in 1941-1942 and in 1942-1943 in Treated and in Control Patients with Acute Infections of the Respiratory Tract*

| Period of Observation | Number of Infections | | Average Duration of Fever after First Day's Treatment | | Frequency* of Primary Rise in Temperature | | Frequency* of Secondary Rise in Temperature | | Frequency* of Hospitalization After First Day's Treatment | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Treated | Controls | Treated | Controls | Treated | Controls | Treated | Controls | Treated | Controls |
| December 1941 to May 1942 | 82 | 80 | 1.1 days | 3.1 days | 4.9 | 22.5 | 14.6 | 27.5 | 2.4 | 15.0 |
| May 1942 to May 1943 | 146 | 104 | 1.1 days | 2.3 days | 6.1 | 12.5 | 14.4 | 26.9 | 2.7 | 12.5 |
| Total | 228 | 184 | 1.1 days | 2.7 days | 5.7 | 16.8 | 14.5 | 27.2 | 2.6 | 13.6 |

* The frequency is stated on the basis of the percentage of infections in which the given condition occurred.

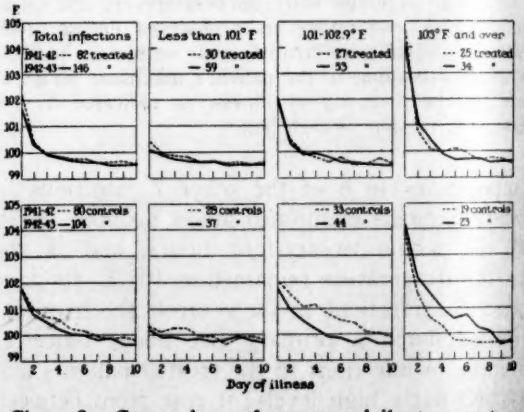


Chart 2.—Comparison of average daily temperatures in infections of the respiratory tract observed during 1941-1942 and 1942-1943 in sulfadiazine-treated and untreated patients arranged according to the patient's maximum temperature on the first day of illness. In the control patients about 25 per cent of the illnesses which began with temperatures of 103 F. or over were treated with sulfadiazine and had to be excluded from the study. The remaining infections constituted a selected number of illnesses which were not representative of the original group.

treated and control inmates.[2e] Although no illnesses were directly traced to this organism, it is noteworthy that both it and hemolytic streptococci were cultured from the bronchial exudate obtained at autopsy. The illness started with a typical scarlatinal rash and an overwhelming pulmonary infection, which was the outstanding feature of the disease. Sulfadiazine therapy was employed at the onset of symptoms and continued for sixteen days, without noticeable effects at any time. A daily dose of 2 to 2.5 Gm. was used. The level of free sulfadiazine in the blood fluctuated between 7.2 and 10.7 mg. per hundred cubic centimeters with a daily maintenance dose of 2 Gm. Postmortem examination revealed extensive bilateral pulmonary consolidation.

## COMMENT

The clinical effects of sulfadiazine described in the foregoing report of results were observed during 1942 and 1943, in the course of studies on the control of acute infections of the respiratory tract. The work was done among the same highly susceptible children observed in the preceding year[1a,b] in order to obtain additional data on the value and limitations of the therapy employed. It followed the same general plan, with the exception that sulfadiazine was employed for a somewhat longer period during each illness in an effort to prevent the secondary rises in temperature attributed to premature withdrawal of the drug. The illnesses observed in 1942 and 1943 were unusually mild among the controls as well as among the treated patients. There were few patients with pneumonia or other bacterial complications. There were no outbreaks of severe infections, such as had occurred in the preceding year and which had been expected again in the highly susceptible group studied.

The results obtained in 1942 and 1943 conformed to the same general pattern as those observed in the preceding year. The illnesses, on the whole, were milder among the drug-treated patients than among the controls. The beneficial effects of drug therapy were measurable by such objective data as reductions in the duration of fever, in the frequency of primary and secondary rises in temperature during the course of illness and in the number of patients requiring hospitalization after the first day's treatment. It usually required at least twenty-four hours before the clinical effects of the drug were clearly noticeable. Some of the illnesses became worse despite therapy, and in others improvement was delayed and apparently unrelated to treatment with sulfadiazine. Secondary rises in temperature occurred as frequently this year as in the past, even though the period of therapy had been prolonged. There were no serious ill effects, despite the repeated and prolonged use of the drug.[1c]

While the results in patients treated with sulfadiazine did not vary greatly from one year to the next, significant differences were noted in the illnesses in the controls. These patients had a decrease in the duration of fever, in the frequency of primary rises in temperature, in the incidence of pneumonia and in the number of infections in which hospitalization was required. Their illnesses were appreciably milder this year than the preceding one, a fact dependent on spontaneous variation from year to year rather than on any measure adopted. The fluctuations in severity seen from time to time in infections in the controls were not observed in infections in treated patients, except for the examples noted. It is possible that the drug may have exerted a stabilizing effect on the course of acute infections of the respiratory tract. If it occurs, such a leveling effect might prove of value in severe infections observed during outbreaks of influenza and other diseases in which drug-susceptible pathogenic bacteria may be involved simultaneously or secondarily.

The unusually mild infections encountered in 1942-1943 might have been attributed to the extensive use of sulfadiazine in the groups studied except for two facts: First, they were observed in the controls as well as in the treated patients; second, they were not limited to the group studied. This group comprised about 5 per cent of the total population of Letchworth Village, while the mildness of infections of the respiratory tract was generalized throughout the institution. Such mild illnesses present no therapeutic problem and therefore do not usually require any form of specific therapy.

Although the sulfonamide compounds are usually unnecessary in the treatment of mild illnesses and apparently valueless in the treatment of purely viral infections of the respiratory tract,[3] the difficulty in practice is to determine at the onset the true nature of the disease and its course. This is particularly true of respiratory illnesses, because the cause is often obscure and the threat of bacterial infection is potentially present. It is frequently difficult, therefore, to anticipate the amount of eventual benefit to be derived from the use of sulfonamide drugs. For the present, reliance must be placed largely on the course of the infections prevalent at the time

3. (*a*) Siegel.[1a] (*b*) Siegel.[1b] (*c*) Rusk, H. A., and van Ravenswaay, A. C.: Sulfadiazine in Respiratory Tract Infections: Its Value in Treatment During Winter of 1942-1943 at Jefferson Barracks, Missouri, J. A. M. A. **122**:495 (June 19) 1943.

and their response to the sulfonamide compounds, on the susceptibility of the patients to bacterial infections and their tolerance for the sulfonamide drugs and on the actual conditions observed in the patient under treatment.

The indiscriminate application of the sulfonamide drugs now available is admittedly inadvisable, because of their ineffectiveness in certain cases, their toxicity and the dangers inherent in the development of resistant bacteria.[4] The apparent ease with which drug-sensitive strains of Neisseria and of pneumococci, for example, may become drug-resistant in vivo and then subsequently spread throughout an exposed population has been demonstrated at Letchworth Village.[2b, c, e]

Results in controlled studies on the use of sulfonamide drugs in acute infections of the respiratory tract will depend, in part, on the role of drug-sensitive bacteria. This is highly variable and fluctuates with conditions about which there is insufficient knowledge. When drug-susceptible bacteria take little or no part in the clinical effects produced by the infection questionable, if any, advantage may be expected from the use of sulfonamide drugs and there should be no important difference between illnesses in drug-treated and in untreated patients. Such results were observed at various times at Letchworth Village [1a,c] and elsewhere [3c] and indicate that the causative agent was probably a virus resistant to the action of the drug. On the other hand, when bacteria sensitive to the sulfonamide drugs contribute materially to the clinical infection beneficial effects can be anticipated during the period of drug therapy and a significant difference between the control and the test group should be observed. Such results were seen at various times at Letchworth Village.[1a,b] The differences between the treated and the untreated group were most evident during an outbreak of severe infections in January and February 1942 and less evident at other times, depending on the degree of effective bacteriostasis exerted by sulfadiazine. It seems clear, therefore, that since the bacterial element in acute respiratory illnesses is highly inconstant, variable differences between a treated and a control group are to be expected.

4. Frisch, A. W.; Price, A. E., and Myers, G. B.: Type VIII Pneumococcus: Development of Sulfadiazine Resistance, Transmission by Cross Infection, and Persistence in Carriers, Ann. Int. Med. **18**:271 (March) 1943.

## SUMMARY

Clinical data have been obtained on the use of sulfadiazine in the treatment of the common acute respiratory illnesses among highly susceptible children observed for eighteen months, from December 1941 to May 1943. The results observed during the last twelve months, which were presented in detail here, are similar to those obtained during the first six months of the study, which were reported previously.

The illnesses were milder, on the whole, in the drug-treated groups than in the untreated groups, with the exceptions noted in outbreaks of uncomplicated infections presumably of viral origin and in sporadic infections during the period studied. The beneficial effects were attributed to the bacteriostatic action of sulfadiazine on the susceptible bacteria primarily or secondarily involved.

The extent of the differences observed between the untreated and the treated groups varied considerably and depended largely on the nature and severity of the infections.

Although the severity of the illnesses in the control group fluctuated with the year to year variations in severity of infections prevalent at the time, the infections in the treated group appeared to be relatively mild during the period of observation. The drug, therefore, seemed to exert a stabilizing effect on the course of acute infections of the respiratory tract. Such an effect might prove to be of value during severe outbreaks of influenza and other respiratory diseases in which drug-susceptible bacteria may be primarily or secondarily implicated.

The physicians at Letchworth Village, particularly Dr. Harry C. Storrs, Superintendent, Dr. Nathaniel Bernstein and Dr. Edward F. Malecki, aided in this work.

The sulfadiazine was supplied by Lederle Laboratories, Inc., Pearl River, N. Y.

Foot of East Fifteenth Street.

# SERUM TOCOPHEROL

## ITS RELATION TO FAILURE OF VITAMIN E THERAPY FOR PSEUDOHYPERTROPHIC MUSCULAR DYSTROPHY

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During the last ten years it has been abundantly demonstrated that vitamin E, in addition to being important in reproduction, is essential for the normal development and metabolism of skeletal muscles. The evidence of this function has been summarized recently in an excellent review by Pappenheimer.[1] There are many points of similarity between the muscular dystrophy seen in patients and the muscular changes which develop when growing animals are deprived of vitamin E. Common to both conditions is creatinuria which becomes more severe as dystrophy progresses. There are also many striking similarities in the chemical and histologic changes demonstrable in muscles which have undergone deterioration in the two conditions.

When vitamin E is restored to animals with nutritional dystrophy there is a prompt decrease in creatinuria and a more gradual restoration of normal chemical constituents and of normal function in the affected muscles. It is natural that observation of the reactions in experimental animals stimulated thinking along the line that a deficiency or a failure of utilization of vitamin E might play a role in clinical dystrophies of as yet unknown cause. So little is known about the human requirements for vitamin E or the levels of tocopherol maintained in the serums of normal persons that the most feasible step toward testing the validity of such a hypothesis was to try the therapeutic effect of vitamin E in clinical dystrophy. The first reports on the therapeutic value of vitamin E, which appeared in 1940 and 1941,[2] described improved muscular function in patients with progressive muscular dystrophy following the administration of wheat germ oil as a supplemental source of the vitamin. These clinical observations stimulated similar and more extensive studies in many laboratories, including our own. Our experience in the treatment of patients with pseudohypertrophic muscular dystrophy is in complete accord with the more recently published papers,[3] which describe consistently negative results in spite of the prolonged administration of liberal amounts of various preparations rich in vitamin E. These reports furnish ample evidence that treatment with vitamin E does not serve to correct whatever disorder of metabolism exists in clinical muscular dystrophy.

From the Department of Pediatrics, Vanderbilt University Medical School.

This work was aided by a grant from the John and Mary R. Markle Foundation.

1. Pappenheimer, A. M.: Muscular Disorders Associated with Deficiency of Vitamin E, Physiol. Rev. **23**:37, 1943.

2. (*a*) Bicknell, F.: Vitamin E in the Treatment of Muscular Dystrophies and Nervous Diseases, Lancet **1**:10, 1940. (*b*) Stone, S.: Treatment of Muscular Dystrophies and Allied Conditions: Preliminary Report on Use of Vitamin E (Wheat Germ Oil), J. A. M. A. **114**:2187 (June 1) 1940; (*c*) Vitamin E in the Treatment of Muscle Disorders of Infancy and Childhood, J. Pediat. **18**:310, 1941. (*d*) Wechsler, I. S.: Treatment of Amyotrophic Lateral Sclerosis with Vitamin E (Tocopherols), Am. J. M. Sc. **200**:765, 1940.

3. (*a*) Shelden, C. H.; Butt, H. R., and Woltman, H. W.: Vitamin E (Synthetic Alpha Tocopherol) Therapy in Certain Neurological Disorders, Proc. Staff Meet., Mayo Clin. **15**:577, 1940. (*b*) Ferrebee, J. W.; Klingman, W. O., and Frantz, A. M.: Vitamin E and Vitamin $B_6$: Clinical Experience in the Treatment of Muscular Dystrophy and Amyotrophic Lateral Sclerosis, J. A. M. A. **116**:1895 (April 26) 1941. (*c*) McBryde, A., and Baker, L. D.: Vitamin Therapy in Progressive Muscular Dystrophy, J. Pediat. **18**:727, 1941. (*d*) Fitzgerald, G., and McArdle, B.: Vitamins E and $B_6$ in the Treatment of Muscular Dystrophy and Motor Neurone Disease, Brain **64**:19, 1941. (*e*) De Jong, R. N.: Vitamin E and Alpha Tocopherol Therapy of Neuromuscular and Muscular Disorders, Arch. Neurol. & Psychiat. **46**:1068 (Dec.) 1941. (*f*) Harris, M. M.: Negative Therapeutic and Metabolic Effects of Synthetic Alpha-Tocopherol (Vitamin E) in Muscular Dystrophy, Am. J. M. Sc. **202**:258, 1941. (*g*) Pohl, J. F., and Baethke, D.: Vitamin E in Progressive Muscular Dystrophy: Failure of Oral Administration in Fifteen Cases, Am. J. Dis. Child. **64**:455 (Sept.) 1942. (*h*) Hawke, W. A.: Vitamin Therapy of Muscular Dystrophy, Canad. M. A. J. **47**:153, 1942. (*i*) Lubin, A. J.: The Use of Alpha Tocopherol in the Treatment of Neuromuscular Disorders, Arch. Int. Med. **69**:836 (May) 1942. (*j*) Schwarz, G. A.; Gammon, G. D., and Masland, R. L.: The use of d-*l* Alpha-Tocopherol Acetate (Synthetic Vitamin E) in Various Neuromuscular Disturbances, J. Nerv. & Ment. Dis. **96**:286, 1942. (*k*) Alpers, B. J.; Gaskill, H. S., and Cantarow, A.: The Effect of Vitamin E on the Muscular Dystrophies, ibid. **96**:384, 1942.

It seemed to us that lack of therapeutic effect, however often confirmed, did not rule out the possibility of a deficiency secondary to some anomaly of absorption or excretion of the vitamin or to chemical destruction of biologically active tocopherol. We have therefore spent a considerable amount of time and effort in order to supplement our therapeutic studies with comparative quantitative determinations of the concentrations of tocopherol in the blood serums of boys with pseudohypertrophic muscular dystrophy and of normal children of similar age.

The present paper, which serves to introduce other studies to be published later, contains a brief summary of our negative therapeutic results and the data obtained in our determination of the concentration of tocopherol in blood serum.

## SUMMARY OF MEDICATION AND CLINICAL OBSERVATIONS

We have had 8 boys with typical pseudohypertrophic muscular dystrophy who were sufficiently cooperative and who resided near enough to our clinic to serve as satisfactory subjects for prolonged observation under treatment. These patients ranged in age from 5 to 19 years. The duration of the disease (the interval since the recognition of muscular weakness) varied from one to sixteen years. The degrees of disability varied from merely an awkward gait and difficulty on rising from a stooped position to almost complete helplessness. Experimental therapy was continued for periods of seven to eighteen months. Before treatment was started and for occasional short periods thereafter the patients were hospitalized, to enable us to make chemical studies and to obtain a more accurate evaluation of their condition. The rest of the time they lived at home, where they were visited frequently to insure their continued cooperation. All of the patients were on a general diet that was adequate in quantity and quality.

A considerable variety of preparations containing vitamin E was purposely employed in the course of our studies. Most of the favorable results reported had occurred in patients given wheat germ oil. It seemed desirable, therefore, to include several weeks of treatment with this and other fairly crude preparations from natural sources on the chance that some fortuitous substance other than α-tocopherol had contributed to the reported effectiveness. For more intensive oral therapy and for intramuscular injections pure synthetic products were used. Usually each patient had courses of several weeks of oral administration of wheat germ oil, concentrated natural tocopherols and synthetic dl-α-tocopherol acetate.[4] The regular daily dose of wheat germ oil was 2 tablespoons for the patients 5 years old and 3 tablespoons for the older boys. The rate of administration of the natural concentrates and of the pure tocopherol acetate varied at different times in the course of an individual experiment from as low as 50 to 75 mg. per day to 250 to 300 mg. per day during short periods of more intensive medication. In addition to oral medication 2 patients received daily intramuscular injections of 50 mg. of alpha tocopherol in oil for one month and 1 boy received 100 mg. daily by this route for three weeks. No intolerance, even to heavy medication, was observed in any patient.

Data in regard to the amounts of tocopherol administered and our clinical observations are collected in table 1. Only the tocopherol given in the form of concentrates or as pure alpha tocopherol is included in the estimated total. The calculation is based on the contents of tocopherol as stated by the manufacturers of the various preparations used. It is of course recognized that the distillates of natural products contain other less active tocopherols as well as alpha tocopherol. No quantitative estimate was made of the vitamin furnished in wheat germ oil, but the oil used was shown to be highly efficient in protecting animals on a diet otherwise deficient in vitamin E. Although little is known in regard to the dietary requirements of children for vitamin E, the data presented leave no doubt that for long periods our patients were provided with alpha tocopherol in amounts far in excess of what would be provided in any ordinary diet which would maintain satisfactory growth and development in normal children.

Our clinical observations forced us to conclude that the administration of vitamin E had no appreciable effect on the course of pseudohypertrophic muscular dystrophy in these 8 patients. Occasionally, for brief periods, it appeared that there might be some slight improvement. This generally occurred when a child who had been bored and discouraged at home was given a period of hospitalization, companionship and

4. The following preparations of vitamin E were used. All were furnished to us without cost by the companies responsible for their manufacture.

Wheat germ oil and fortified Fyvee wheat germ oil were furnished by General Mills, Inc., Minneapolis. Tofaxin, a distillate of natural tocopherols from wheat germ oil, was furnished by Winthrop Chemical Company, Inc., New York. Eprolin, a distillate of natural tocopherols, was furnished by Eli Lilly and Company, Indianapolis. Ephynal acetate, synthetic dl-α-tocopherol acetate tablets and dl-α-tocopherol in oil for intramuscular injection, were furnished by Hoffman-La Roche, Inc., Nutley, N. J.

more attention coincident with medication. Such a patient showed improved morale and made a greater effort to use what strength he had. However, the questionable improvement observed in these periods was usually not maintained and was never progressive. In some patients there was uninterrupted and fairly rapid deterioration throughout the period of observation.

In order to have a more objective criterion of the effect of medication, determinations of urinary creatine and creatinine, by the method of Folin,[5] were carried out before treatment was started and at later intervals during the period of observation. A prompt and consistent change observed when curative amounts of vitamin E are restored to an animal with nutritional dystrophy is a distinct decrease in the amount of creatine excreted.[6] Presumably one would expect to find a significant reduction in the creatinuria in persons with clinical dystrophy if the administration of the vitamin had a favorable influence. Before treatment all our patients showed the low excretion of preformed creatinine characteristic of muscular dystrophy, with outputs of creatine which, in different patients, amounted to 45 to 70 per cent of the total creatinine excreted. In no instance did the administration of vitamin E have any significant effect on the degree of creatinuria. Since this finding is in accord with the data already published,[7] our figures are not presented in greater detail. All these observations furnish further evidence that the pathologic processes of clinical muscular dystrophy are uninfluenced by the administration of vitamin E.

TABLE 1.—*Summary of Data on Therapeutic Trial of Vitamin E in 8 Patients with Pseudohypertrophic Muscular Dystrophy*

| Patient | Age, Yr. | Duration of Disease, Yr. | Total Duration of Therapy, Mo. | Total Tocopherol Exclusive of That in Wheat Germ Oil, Gm. | Duration of Treatment with Wheat Germ Oil, Wk. | Comment |
|---|---|---|---|---|---|---|
| H. J. | 19 | 16 | 13 | 23.7 | None | Patient confined to wheel chair and bed; could not stand alone or turn self in bed; no change in condition |
| H. H. | 12 | 6 | 18 | 16.8 | 8 | At start could walk with great difficulty, but could not rise from stooped position or go up or down a step; no improvement at any time; at end of treatment no longer tried to walk; had intramuscular therapy for one month, 50 mg. daily |
| J. L. | 5 | 2 | 16 | 21.7 | 6 | Showed rapid deterioration during observation period; walked fairly well at start, but had difficulty rising from stooped position; by end of period unable to walk; confined to bed and wheel chair |
| Cl. S. | 11 | 7 | 16 | 29.5 | 20 | Had been bedridden before admission; improved or encouraged to point of walking awkwardly and getting around in wheel chair; improvement maintained but not progressive; intramuscular injections for one month, 50 mg. daily |
| Ch. S. | 5 | 1 | 14 | 21.0 | 20 | Early stage; had fair degree of activity but awkward gait, "climbs up himself"; large calf muscles; little change during period of observation |
| W. S. | 11 | 3 | 9 | 3.9 | 35 | Helpless, obese, bedridden; cannot rise to sitting position without help; no improvement; intramuscular injections for three weeks, 100 mg. daily |
| J. A. | 5 | 1-2 | 7 | 6.0 | 15 | Progressive weakness for last year; awkward, cannot rise from sitting position; disease progressed during treatment |
| J. N. | 10 | 8-10 | 10 | 24.0 | 25 | Slight difficulty since starting to walk, rapid deterioration in last year; now crawls on floor; cannot stand; growing rapidly; no improvement in strength |

## STUDIES OF THE TOCOPHEROL CONTENT OF BLOOD SERUM

There was no doubt that exceedingly liberal amounts of tocopherol had been furnished our patients in the course of our therapeutic studies. Nevertheless, the question constantly recurred whether we had actually succeeded in maintaining in them concentrations of tocopherol as high as are present in normal children. The only feasible approach to such a comparison appeared to be the chemical determination of the tocopherol content of blood serum. The quantitative estimation of tocopherol in biologic material is beset with many difficulties inherent in the necessity of separation from interfering substances and protection from oxidation during the course of manipulation. A detailed description of the pro-

5. Folin, O.: On the Determination of Creatinine and Creatine in Urine, J. Biol. Chem. **17**:469, 1914.

6. (*a*) Verzár, F.: Der Creatin-Stoffwechsel bei der Muskeldystrophie durch E-Vitamin-Mangel und seine Beeinflussung durch Tocopherol, Ztschr. f. Vitaminforsch. **9**:242, 1939. (*b*) MacKenzie, C. G., and McCollum, E. V.: The Cure of Nutritional Muscular Dystrophy in the Rabbit by Alpha Tocopherol and Its Effect on Creatine Metabolism, J. Nutrition **19**:345 1940.

7. (*a*) Harris.[3f] (*b*) Lubin.[3l] (*c*) Alpers.[3k] (*d*) Fleischmann, W.: Creatine-Creatinine Excretion in Neuromuscular Diseases Treated with Alpha Tocopherol and Testosterone, Proc. Soc. Exper. Biol. & Med. **46**:94, 1941.

cedure finally adopted will be published elsewhere. In brief, the colorimetric method described by Emmerie and Engel [8] was used after the incorporation of various modifications suggested by Mayer and Sobotka [9] and by Mattill and his co-workers.[10] Photoelectric measurements were made of the color produced when ferric iron is reduced by tocopherol in the presence of α-α-dipyridyl. With pure solutions of alpha tocopherol the color produced follows Beer's law over a considerable range of concentrations. Tocopherol added to blood serum could be satisfactorily recovered. The method measures only unoxidized tocopherol and does not distinguish between the alpha form and the tocopherols which are less active biologically. The reaction is not sufficiently specific to make it certain that the color obtained in extracts from blood may not be contributed to by substances other than tocopherols. However, the fact that with the procedure used the color produced by extracts of serum from animals with vitamin E deficiency was slight and increased promptly with the administration of tocopherol indicates that we were measuring the level of unoxidized tocopherol with considerable accuracy.

TABLE 2.—*Tocopherol Content of Blood Serum of Boys with Progressive Muscular Dystrophy*

| Patient | Age, Yr. | Supplemental Vitamin E | Serum Tocopherol, Mg./100 Cc. |
|---|---|---|---|
| H. J. | 21 | None for two years | 0.97 |
| H. J. | 21 | 160 mg. eprolin daily for ten days | 1.35 |
| H. H. | 13 | None for a year | 1.02 |
| H. H. | 13 | 50 mg. ephynal acetate daily for ten days | 1.47 |
| W. N. | 9 | Never treated | 1.28 |
| W. N. | 9 | 120 mg. tocopherol for six days | 1.53 |
| J. A. | 6 | 1 tablespoon wheat germ oil daily | 1.22 |
| J. L. | 9 | None for two years | 0.73 |
| H. Je. | 12 | Never treated | 0.80 |
| J. N. | 12 | None for a year | 0.81 |

The figures presented in table 2 were obtained more than a year after our therapeutic studies were completed. Five of the patients with muscular dystrophy had been subjects for the earlier observations. At the time when the tocopherol studies were made 4 of them had received no supplemental vitamin E for over a year. One (J. A.) was taking one tablespoon of wheat germ oil daily to satisfy his mother's demands for some form of medication. Patients H. Je. and W. N. had never been treated. For comparison, table 3 contains a small series of figures obtained for the blood serums of children without muscular disease. We regret that the difficulties of transportation have made it impracticable at the present time for us to extend our studies to include a greater number of patients. Certainly if lack of alpha tocopherol were playing any constant or essential role in the causation of clinical dystrophy a deficiency would have been detected in a study of even as few as 7 typical cases. On the contrary, the levels of 0.73 to 1.28 mg. per hundred cubic centimeters for serums of patients with untreated dystrophy are in close agreement with the range of 0.64 to 1.12 mg. per hundred cubic centimeters found for the serums of children without muscular disease. These levels of tocopherol are also essentially the same as those found by Wechsler, Mayer and Sobotka [11] in the serums of adults. After the initial levels were determined, 3 of the patients with dystrophy were given vitamin E in approximately the same daily doses that had been administered for a period of months during the earlier therapeutic study. After a few days of such treatment the levels of tocopherol in the serums of the patients showed significant increases over the initial values. Thus we can conclude that our negative clinical results were observed in spite of medication which must have maintained the level of the tocopherol in the blood somewhat higher than the usual normal range for long periods.

TABLE 3.—*Tocopherol Content of Blood Serum of Children Without Muscular Dystrophy*

| Subject | Age, Yr. | Sex | Diagnosis | Serum Tocopherol, Mg./100 Cc. |
|---|---|---|---|---|
| H. B. | 15 | M | No disease | 0.72 |
| L. J. | 11 | M | Behavior problem | 0.94 |
| J. H. | 13 | M | Allergy | 1.12 |
| M. E. | 9 | F | No disease | 0.88 |
| J. L. | 11 | M | No disease | 0.98 |
| A. G. | 5 | M | Respiratory infection | 1.02 |
| J. C. | 5 | F | Celiac disease | 0.64 |
| F. C. | 14 | F | Otitis media | 0.82 |
| H. B. | 9 | M | Bronchitis | 0.79 |

## COMMENT

The data presented make it evident that patients with muscular dystrophy have neither a primary lack of vitamin E nor a deficiency secondary to poor absorption or chemical destruc-

8. Emmerie, A., and Engel, C.: Colorimetric Determination of Tocopherol (Vitamin E): III. Estimation of Tocopherol in Blood Serum, Rec. trav. chim. des Pays-Bas **58**:895, 1939.

9. Mayer, G. G., and Sobotka, H.: Photoelectric Determination of d-l Alpha Tocopherol in Serum, J. Biol. Chem. **143**:695, 1942.

10. (*a*) Devlin, H. B., and Mattill, H. A.: The Chemical Determination of Tocopherols in Muscle Tissue, J. Biol. Chem. **146**:123, 1942. (*b*) Hines, L. R., and Mattill, H. A.: The Chemical Determination of Tocopherols in Liver and Muscle: Tocopherols in Urine and Feces, ibid. **149**:549, 1943.

11. Wechsler, I. S.; Mayer, G. G., and Sobotka, H.: Tocopherol Level in Serum of Normals and Patients with Amyotrophic Lateral Sclerosis, Proc. Soc. Exper. Biol. & Med. **47**:152, 1941.

tion of tocopherol. Under these conditions it is not surprising that consistently negative clinical results are obtained by numerous investigators who have treated patients with muscular dystrophy with vitamin E. However, more information must be obtained before the broader concept of the possible existence of a similar fundamental metabolic defect in nutritional and clinical dystrophies can be dismissed. Recent work of Houchin [12] indicates that it is probably necessary for alpha tocopherol to be phosphorylated or otherwise activated before it plays its essential biologic role in tissue metabolism. It is conceivable that some interference with such intermediate steps blocks the effectiveness of tocopherol in the muscles of patients with clinical dystrophy and so brings about essentially the same metabolic failure as occurs in animals deprived of vitamin E.

12. Houchin, O. B.: The in Vitro Effect of Alpha Tocopherol and Its Phosphate Derivative on Oxidation in Muscle Tissue, J. Biol. Chem. **146**:313, 1942.

## SUMMARY AND CONCLUSIONS

Prolonged medication with liberal amounts of various preparations of vitamin E failed to improve the clinical condition or to decrease the creatinuria in 8 patients with pseudohypertrophic muscular dystrophy.

In studies of the tocopherol content of blood serum a range of 0.73 to 1.28 mg. per hundred cubic centimeters was found for untreated patients with muscular dystrophy, as compared with values of 0.64 to 1.12 mg. per hundred cubic centimeters for children of similar age without muscular disease.

Following the administration of vitamin E to patients with dystrophy there was a prompt and significant rise in the level of tocopherol in the blood serum.

The conclusion seems justified that the administration of supplemental vitamin E to patients with muscular dystrophy is an unnecessary and useless procedure.

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# ASCORBIC ACID, RIBOFLAVIN AND THIAMINE CONTENT OF COW'S MILK

## INFLUENCE OF THE RATION

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With the present curtailment of the supply of meat and meat products more reliance must be placed on milk as a protective food in the human diet. The data that have been obtained from numerous investigations of the nutritive value of milk show that it contains protein of high biologic value, fat which can be completely digested and minerals and vitamins that are extremely important in the daily diet, particularly in the diet of small children. Since milk is such an important food, many studies have been made of the factors that influence its nutritive value; and it is generally agreed that under normal conditions changing a cow's ration does not cause any significant changes in the protein, fat and mineral composition of the milk. However, a review of the literature shows that there is lack of agreement regarding the effect of changing a cow's ration on the vitamin content of the milk. The literature which deals with this subject is voluminous, and, for convenience, it will be discussed under separate headings.

### LITERATURE

*Ascorbic Acid.*—Hart, Steenbock and Ellis [1] reported that the milk from cows on summer pasture was much richer in ascorbic acid than that from cows given dry feed or that produced in the winter. Hess, Unger and Supplee [2] found that the milk from cows after they had had three weeks' pasturage was much richer in ascorbic acid than milk from the same cows when they were fed dry fodder. According to MacLeod [3] the high value for ascorbic acid of milk from pasture-fed cows is due to the fact that fresh grasses are rich in ascorbic acid. Hannisdahl [4] stated that the milk from pasture-fed cows contained more ascorbic acid than that from stall-fed cows. Dutcher, Eckles, Dahle, Mead and Schaefer [5] concluded that the ascorbic acid content of cow's milk is dependent on the ascorbic acid content of the ration ingested by the cow. Rasmussen, Guerrant, Shaw, Welch and Bechdel [6] found that after a cow has lactated for two months the ascorbic acid content of the milk is apparently dependent solely on the ascorbic acid content of the ration. Olson and Copeland [7] stated the belief that the ascorbic acid in milk has its origin in the cow's ration and that ensilage is an important source. These reports are in agreement and indicate that the composition of a cow's ration has a definite influence on the ascorbic acid content of the milk.

Several investigators have reported contradictory results. Kon and Watson [8] concluded that the nutrition of a cow has no effect on the amount of ascorbic acid in the milk. Garrett, Arnold and Hartman [9] found the same amount of ascorbic acid in milk when cows were fed alternately beet pulp, corn and molasses-grass

Contribution no. 500 from Massachusetts State College and Agricultural Experiment Station.

1. Hart, E. B.; Steenbock, H., and Ellis, N. R.: Influence of Diet on the Antiscorbutic Potency of Milk, J. Biol. Chem. **42**:383-396, 1920.

2. Hess, A. F.; Unger, L. J., and Supplee, G. C.: Relation of Fodder to the Antiscorbutic Potency and Salt Content of Milk, J. Biol. Chem. **45**:229-235, 1921.

3. MacLeod, F. L.: Antiscorbutic Vitamin Content of Milk of Stall-Fed Cows Through a Year, J. A. M. A. **88**:1947-1949 (June 18) 1927.

4. Hannisdahl, B.: Cow's Milk as a Source of Vitamin C, Tidsskr. f. d. norske lægefor. **57**:1068, 1937; Nutrition Abstr. & Rev. **8**:89, 1938.

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6. Rasmussen, R.; Guerrant, N. B.; Shaw, A. D.; Welch, R. C., and Bechdel, S. I.: The Effects of Breed Characteristics and Stages of Lactation on the Vitamin C (Ascorbic Acid) Content of Cow's Milk, J. Nutrition **11**:425-432, 1936.

7. Olson, T. M., and Copeland, L.: The Influence of Pasteurization and Diet of the Cow on the Antiscorbutic Potency of the Milk, J. Dairy Sc. **7**:370-380, 1924.

8. Kon, S. K., and Watson, M. B.: The Vitamin C Content of Cow's Milk, Biochem. J. **31**:223-226, 1937.

9. Garrett, O. F.; Arnold, R. B., and Hartman, G. H.: Some Factors Affecting Certain Milk Properties: III. Effect of Roughages on Ascorbic Acid, J. Dairy Sc. **23**:47-52, 1940.

silage as roughage. Guggenheim,[10] Riddell, Whitnah, Hughes and Lienhardt[11] and Hughes, Fitch, Cave and Riddell[12] concluded that the ascorbic acid content of a cow's ration has little if any influence on the ascorbic acid content of the milk. West and Wenger[13] reported that there was no appreciable change in the ascorbic acid content of milk when corn silage was eliminated from a cow's ration. Whitnah and Riddell[14] fed cows 65 Kg. per day of green rye which contained 0.86 mg. of ascorbic acid per gram for fifteen days and found no increase in the ascorbic acid content of the milk. Reedman[15] reported that dairy cattle can synthesize ascorbic acid and therefore are not susceptible to vitamin C deficiency. However, Knight, Dutcher, Guerrant and Bechdel[16] assayed the contents of the rumen of a cow after feeding 100 Gm. and 150 Gm. of ascorbic acid mixed with corn silage and also after administering 100 Gm. of ascorbic acid through a fistula in the rumen and found rapid destruction of the ascorbic acid, with complete destruction in less than two hours.

A number of investigators have noted a seasonal variation in the ascorbic acid content of milk. Rohmer, Bezssonoff and Stoerr[17] found that the ascorbic acid content of milk was high in November and dropped sharply from then until March. Whitnah and Riddell[14] stated that the ascorbic acid content of cow's milk increased from October to December, then decreased until February and again increased until March. Holmes, Tripp, Woelffer and Satterfield[18] reported seasonal variation in the content of ascorbic acid, with a peak in early November and another in February. Guggenheim[10] showed that milk produced in Palestine contained considerably more ascorbic acid during the second than during the first half of the year, with a peak in July. Trout and Gjessing[19] found the ascorbic acid content of milk lowest in winter and highest in summer. In connection with the seasonal variations of the ascorbic acid of cow's milk, it is interesting to note that Sinkko[20] observed a seasonal variation in the ascorbic acid content of human milk, with the highest content in August and September. Incidentally, he also noted that stillbirths and infant mortality were lowest at the season of the year when the mothers were less likely to be deficient in ascorbic acid. On the other hand, Sharp[21] reported that the ascorbic acid content of fresh cow's milk was relatively constant throughout the year. Schwartze, Murphy and Hann[22] concluded that winter milk from ensilage-fed cows contained as much ascorbic acid as the best summer milk from cows on pasturage. Kon and Watson[8] found that the amount of vitamin C in mixed milk was constant and independent of the season of the year. MacLeod[3] found no seasonal variation in the ascorbic acid content of milk when cows were given a well balanced ration throughout the year.

*Riboflavin.*—Considerable attention has been given to the influence of cows' rations on the riboflavin content of milk. Hand and Sharp[23] found that milk from pasture-fed cows contained 20 per cent more riboflavin than milk from cows fed typical winter rations. Houston, Kon and Thompson[24] reported that raw winter milk

10. Guggenheim, K.: Seasonal Fluctuations of the Vitamin A and C Content of Palestinian Milk, J. Hyg. **40**:690-697, 1940.

11. Riddell, W. H.; Whitnah, C. H.; Hughes, J. S., and Lienhardt, H. F.: Influence of the Ration on the Vitamin C Content of Milk, J. Nutrition **11**:47-54, 1936.

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13. West, F. V., and Wenger, J. C.: The Vitamin C Content of Certified Milk at the Time of Consumption, Am. J. Digest. Dis. **5**:251-252, 1938.

14. Whitnah, C. H., and Riddell, W. H.: Variations in the Vitamin C Content of Milk, J. Dairy Sc. **20**:9-14, 1937.

15. Reedman, E. J.: The Ascorbic Content of Milk, Canad. Pub. Health J. **28**:339-340, 1937.

16. Knight, C. A.; Dutcher, R. A.; Guerrant, N. B., and Bechdel, S. I.: Destruction of Ascorbic Acid in the Rumen of the Dairy Cow, Proc. Soc. Exper. Biol. & Med. **44**:90-93, 1940.

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18. Holmes, A. D.; Tripp, F.; Woelffer, E. A., and Satterfield, G. H.: A Study of Breed and Seasonal Variations in the Ascorbic Acid Content of Certified Milk from Guernseys and Holsteins, J. Nutrition **17**: 187-198, 1939.

19. Trout, G. M., and Gjessing, E. C.: Ascorbic Acid and Oxidized Flavor in Milk: I. Distribution of Ascorbic Acid and Occurrence of Oxidized Flavor in Commercial Grade A Raw, in Pasteurized Irradiated, and in Pasteurized Milk Throughout the Year, J. Dairy Sc. **22**:271-281, 1939.

20. Sinkko, E. I.: Relation Between Infantile Mortality, Stillbirth and Variations in the Vitamin C Content of the Mother's Milk at Various Seasons of the Year in Finland, Acta pædiat. **21**:407-427, 1937; abstracted, Nutrition Abstr. & Rev. 1938 **8**:201, 1938.

21. Sharp, P. F.: Vitamin C in Pasteurized Milk, Science **84**:461-462, 1936.

22. Schwartze, E. W.; Murphy, F. J., and Hann, R. M.: Studies on the Destruction of Vitamin C in the Boiling of Milk, J. Nutrition **2**:325-352, 1930.

23. Hand, D. B., and Sharp, P. F.: The Riboflavin Content of Cow's Milk, J. Dairy Sc. **22**:779-783, 1939.

24. Houston, J.; Kon, S. K., and Thompson, S. Y.: The Effect of Commercial Pasteurization and Sterilization on the Vitamin $B_1$ and Riboflavin Content of Milk as Measured by Chemical Methods, J. Dairy Research **11**:67-70, 1940.

(February) contained 0.96 mg. of riboflavin per liter as compared with 1.4 and 1.9 mg. for summer milk (June and July). In a later publication [25] they stated that winter milk contained 1.1 mg. and summer milk 1.5 mg. of riboflavin per liter and that there was a definitely higher amount in milk produced from grass. Kon [26] found from 20 to 50 per cent more riboflavin in summer milk than in winter milk and stated "there is good evidence to show that the increase is due to pasture." According to Whitnah, Kunerth and Kramer [27] the riboflavin content of milk was high in July, after the cows had been fed a pasture ration. Kramer, Dickman, Hildreth, Kunerth and Riddell [28] assayed the milk produced by a herd during and after a severe drought. The milk produced after rains had caused an abundance of young green grass contained 25 per cent more riboflavin than that produced during the drought. On the other hand, Riddell [29] reported that cows fed prairie hay and grain or wheat straw and grain produced milk as rich in riboflavin as that produced by well fed cows. Johnson, Maynard and Loosli [30] found little difference in the riboflavin content of milk produced on pasturage or winter rations. The conclusion that the composition of a cow's ration does not influence the riboflavin content of the milk is not surprising, since Wegner, Booth, Elvehjem and Hart,[31] Hunt and his associates [32] and others have shown that cattle synthesize riboflavin in the rumen. Hence a cow might synthesize sufficient riboflavin to enable her to produce milk with a constant content of riboflavin.

*Thiamine.*—The influence of the ration on the thiamine content of cow's milk has been studied by a number of investigators. Hughes, Fitch and Cave [33] obtained more vitamin B [34] from milk of cows fed a vitamin-rich ration than from milk of cows fed a vitamin-poor ration. Kennedy and Dutcher [35] claimed that the vitamin B in cow's milk is entirely dependent on its occurrence in the cow's ration. However, several investigators have expressed the contrary opinions. Osborne and Mendel [36] found that the the vitamin B potency of milk from pasture-fed cows was not superior to that of milk from cows fed a winter ration. Bechdel [37] studied milk produced by cows fed a vitamin B–deficient ration for over two years, including the period of growth, and concluded that vitamin B in milk is not dependent on the presence of this vitamin in the ration. Bechdel, Honeywell, Dutcher and Knutson [38] concluded that Flavobacterium, which comprised 90 per cent of the microflora of the rumen, enabled cows which were fed a vitamin B–deficient ration to produce milk of normal vitamin B content. Hunt and Krauss [39] concluded that fresh tender grass produced milk with a higher content vitamin $B_1$ than that of overly mature pasture grass. Houston, Kon and Thompson [25] reported that the composition of the ration has little or no effect on the vitamin $B_1$ content of milk. McElroy and Goss [40] found appreciable amounts of thiamine in the milk of a fistulated cow with rumen contents containing no thiamine.

25. Houston, J.; Kon, S. K., and Thompson, S. Y.: Vitamin $B_1$ and Riboflavin: III. The Effect of Stage of Lactation and of Season on the Vitamin $B_1$ and Riboflavin Contents of Milk, J. Dairy Research **11**: 155-167, 1940.

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29. Riddell, W. H.: The Vitamin G (Flavin) Content of Milk, Certified Milk **15**:5, 1940.

30. Johnson, P.; Maynard, L. A., and Loosli, J. K.: The Riboflavin Content of Milk as Influenced by Diet, J. Dairy Sc. **24**:57-60, 1941.

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32. Hunt, C. H.; Kiek, C. H.; Burroughs, E. W.; Bethke, R. M.; Schalk, A. F., and Gerlaugh, P.: Riboflavin and Thiamine in the Rumen Content of Cattle, J. Nutrition **21**:85-92, 1941.

33. Hughes, J. S.; Fitch, J. B., and Cave, H. W.: The Quantitative Relation Between the Vitamin Content of Feed Eaten and Milk Produced, J. Biol. Chem. **46**:50, 1921.

34. In the early investigations vitamin $B_1$ or thiamine, was not distinguished from the vitamin B complex.

35. Kennedy, C.; Dutcher, R. A., and Eckles, C. H.: Vitamine Studies: IX. The Influence of the Diet of the Cow upon the Quantity of Vitamines A and B in the Milk, J. Biol. Chem. **50**:339-359, 1922.

36. Osborne, T. B.; Mendel, L. B., and Wakeman, A. J.: Milk as a Source of Water-Soluble Vitamin, J. Biol. Chem. **41**:515-523, 1920.

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39. Hunt, C. H., and Krauss, W. E.: The Influence of the Ration of the Cow upon the Vitamin B and Vitamin G Content of Milk, J. Biol. Chem. **92**:631-638, 1931.

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## EXPERIMENTAL STUDIES

It is evident from the résumé of the literature that investigators are not in agreement concerning the influence of a cow's ration on the amount of ascorbic acid, riboflavin or thiamine in the milk. Furthermore, the literature consulted did not contain any report of the simultaneous influence of the ration on the amount of the three vitamins in the milk. Accordingly, an investigation was undertaken to accumulate additional data in this regard. Since it is generally believed that young, rapidly growing green grass is particularly rich in vitamins, the content of ascorbic acid, riboflavin and thiamine in milk was studied during the interval while the cows were being transferred from the winter ration to green grass, pasture ration.

*Method.*—The milk for the study was carefully selected in order that the data obtained might be applicable for judging the nutritive value of commercially produced milk. Since farm herds in this locality frequently contain more than one breed of cows, the milk used in this study was obtained from several dairy breeds. Moreover, a large number of cows (18 Ayrshires, 14 Guernseys, 18 Holsteins, 12 Jerseys and 7 Shorthorns) was used in order to eliminate any influence of the individual characteristics of the cows. Furthermore, the rations and management of the cows were similar to those of modern, local dairy farms. Each cow was fed 7 pounds (3.2 Kg.) of locally grown hay, 34 pounds (15.4 Kg.) of silage (20 pounds [9.1 Kg.] of corn and 14 pounds (6.4 Kg.) of grass) and 9.5 pounds (4.3 Kg.) of ground grain (14 per cent protein) daily. Detailed information regarding the rations of the same herd of cows during four months previous to the study has been reported by Holmes, Jones, Wertz and Kuzmeski.[41] During period 1, April 26 to May 10 inclusive, the cows were housed in a warm barn and fed the winter rations previously described. From May 11 to June 17 inclusive the cows received fresh, young, rapidly growing green grass. For convenience the time during which the cows were pastured has been divided into two periods, period 2, May 11 to May 26, and period 3, May 27 to June 17. During the first week or two of the first period of pasturage there were several cold, cloudy, windy days and a number of rainy days; hence the cows were not as comfortable as during period 1, when they were housed in a warm barn.

The cows were milked at 3:30 a. m. and 3:30 p. m. The afternoon milk was promptly cooled to 40 F. (5 C.) and held at that temperature overnight. The morning milk was also cooled quickly and then combined with the afternoon milk. About four hours later a representative sample of the combined milk was taken for assay. The assays for riboflavin and ascorbic acid were started at once, but the assay for thiamine was not started for about six hours. The ascorbic acid content of the milk was determined by the procedure reported by Holmes, Tripp, Woelffer and Satterfield,[18] the riboflavin by the method described by Holmes, Jones, Wertz and Kuzmeski [41] and the thiamine by a modification of the Hennessy and Cerecedo [42] thiochrome method.

TABLE 1.—*Influence of the Rations of Cows on the Vitamin Content of Milk (Milligrams per Liter)*

| Period 1 | | | | Period 2 | | | | Period 3 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Sample No. | Ascorbic Acid | Riboflavin | Thiamine* | Sample No. | Ascorbic Acid | Riboflavin | Thiamine* | Sample No. | Ascorbic Acid | Riboflavin | Thiamine* |
| 1 | 20.7 | 1.41 | 0.31 | 12 | 18.9 | 1.37 | 0.27 | 25 | 19.6 | 1.25 | 0.30 |
| 2 | 19.2 | 1.40 | 0.31 | 13 | 19.9 | 1.30 | 0.31 | 26 | 19.6 | 1.29 | 0.38 |
| 3 | 21.5 | 1.45 | 0.31 | 14 | 19.1 | 1.25 | 0.31 | 27 | 19.5 | 1.38 | 0.33 |
| 4 | 19.2 | 1.42 | 0.30 | 15 | 18.6 | 1.24 | 0.31 | 28 | 19.5 | 1.44 | 0.34 |
| 5 | 19.4 | 1.38 | 0.30 | 16 | 18.0 | 1.22 | .... | 29 | 19.9 | 1.48 | 0.38 |
| 6 | 20.7 | 1.36 | 0.34 | 17 | 19.4 | 1.29 | 0.30 | 30 | 19.9 | 1.51 | 0.38 |
| 7 | 20.2 | 1.35 | 0.33 | 18 | 19.1 | 1.51 | 0.34 | 31 | 19.4 | 1.42 | 0.34 |
| 8 | 20.9 | 1.57 | 0.33 | 19 | 18.6 | 1.27 | 0.32 | 32 | 19.9 | 1.47 | 0.32 |
| 9 | 20.9 | 1.40 | 0.33 | 20 | 19.1 | 1.08 | 0.35 | 33 | 19.9 | 1.47 | 0.32 |
| 10 | 20.2 | 1.51 | 0.32 | 21 | 19.6 | 1.21 | 0.31 | 34 | 19.4 | 1.35 | 0.33 |
| 11 | 20.1 | 1.45 | 0.31 | 22 | 19.1 | 1.29 | 0.32 | 35 | 18.9 | 1.89 | 0.32 |
| | | | | 23 | 19.1 | 1.22 | 0.31 | 36 | 19.0 | 1.52 | 0.31 |
| | | | | 24 | 19.5 | 1.19 | 0.34 | 37 | 19.0 | 1.55 | 0.33 |
| Average | 20.3 | 1.43 | 0.32 | Average | 19.1 | 1.26 | 0.32 | Average | 19.5 | 1.46 | 0.34 |

* The amounts of thiamine were calculated as thiamine hydrochloride.

*Results.*—The results of the assays are reported in detail in table 1, and they may be summarized as follows: In period 1 the ascorbic acid content of the milk varied from 19.2 to 21.5 mg. per liter with an average of 20.3 mg.; the values for riboflavin ranged from 1.35 to 1.57 mg. per liter and averaged 1.43 mg., and the values for thiamine were (calculated as thiamine hydrochloride) 0.30 to 0.34 mg. per liter, with an average of 0.32 mg. In period 2 the values were: ascorbic acid, 18.0 to 19.9 mg. per liter, with an average of 19.1; riboflavin, 1.08 to 1.51 mg. per liter, with an average of 1.26, and thiamine hydrochloride, 0.27 to 0.35 mg. per liter, with an average of 0.32. In period 3 the results were: ascorbic acid, 18.9 to 19.9 mg. per liter, with an average of 19.5; riboflavin 1.25 to 1.89 mg. per liter, with an average of 1.46, and

41. Holmes, A. D.; Jones, C. P.; Wertz, A. W., and Kuzmeski, J. W.: The Ratio of Ascorbic Acid, Riboflavin and Thiamin in Raw and Pasteurized Milk, J. Nutrition **26**:337-345, 1943.

42. Hennessy, D. J., and Cerecedo, L. R.: The Determination of Free and Phosphorylated Thiamin by a Modified Thiochrome Assay, J. Am. Chem. Soc. **61**:179-183, 1939.

thiamine hydrochloride, 0.30 mg. to 0.33 mg. per liter, with an average of 0.34 mg.

It will be noted that when the cows were transferred from winter rations to rations of young, fresh grass there was a decrease in the amount of ascorbic acid and riboflavin per liter of milk. The ascorbic acid content of the milk produced during period 3 was higher than that of the milk produced during period 2 but below that of the milk produced from the winter ration. The riboflavin content of the milk was higher during period 3 than during period 2; in fact it was higher then than during the period when the cows received the winter rations. The content of thiamine in the milk was higher during the third period than during either of the first two periods.

values for the three periods were 255.6, 259.0 and 251.1 mg. of ascorbic acid, 18.0, 16.9 and 18.8 mg. of riboflavin and 4.0, 4.3 and 4.4 mg. of thiamine hydrochloride per cow per day.

In this discussion of the relation of the volume of milk produced per cow per day to the total content of ascorbic acid, reference should be made to an earlier study. Holmes, Tripp, Woelffer and Satterfield [43] found that Guernsey cows giving 12 to 13 liters of milk daily with 20 mg. of ascorbic acid per liter and Holstein cows giving 13 to 14 liters daily with 17.9 mg. of ascorbic acid per liter produced an identical quantity of ascorbic acid (241 mg.) daily. However, changes in the volume of milk produced from day to day were not accompanied by corresponding changes in the ascorbic acid content

TABLE 2.—*Average Daily Production per Cow of Ascorbic Acid, Riboflavin and Thiamine*

| Period 1 | | | | | Period 2 | | | | | Period 3 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Sample No. | Milk, L. | Ascorbic Acid, Mg. | Riboflavin, Mg. | Thiamine,* Mg. | Sample No. | Milk, L. | Ascorbic Acid, Mg. | Riboflavin, Mg. | Thiamine,* Mg. | Sample No. | Milk, L. | Ascorbic Acid, Mg. | Riboflavin, Mg. | Thiamine,* Mg. |
| 1 | 13.0 | 269.1 | 18.3 | 4.0 | 12 | 12.7 | 240.0 | 17.4 | 3.4 | 25 | 13.4 | 262.6 | 16.8 | 4.0 |
| 2 | 12.7 | 243.8 | 17.8 | 3.9 | 13 | 13.5 | 268.7 | 17.6 | 4.2 | 26 | 12.8 | 250.9 | 16.5 | 4.9 |
| 3 | 12.4 | 266.6 | 18.0 | 3.8 | 14 | 13.0 | 248.3 | 16.3 | 4.0 | 27 | 13.6 | 265.2 | 18.8 | 4.5 |
| 4 | 12.9 | 247.7 | 18.3 | 3.9 | 15 | 13.5 | 251.1 | 16.7 | 4.2 | 28 | 14.0 | 273.0 | 20.2 | 4.8 |
| 5 | 12.6 | 299.9 | 17.4 | 3.8 | 16 | 13.6 | 244.8 | 16.6 | ... | 29 | 13.3 | 264.7 | 19.7 | 5.1 |
| 6 | 12.5 | 258.8 | 17.0 | 4.3 | 17 | 14.2 | 275.5 | 18.3 | 4.3 | 30 | 12.4 | 246.8 | 18.7 | 4.7 |
| 7 | 12.7 | 256.5 | 17.1 | 4.2 | 18 | 14.0 | 267.4 | 18.3 | 4.8 | 31 | 12.7 | 246.4 | 18.0 | 4.3 |
| 8 | 12.7 | 265.4 | 19.9 | 4.2 | 19 | 13.8 | 256.7 | 17.5 | 4.4 | 32 | 12.7 | 250.7 | 18.7 | 4.1 |
| 9 | 12.7 | 265.4 | 17.8 | 4.2 | 20 | 13.9 | 265.5 | 15.0 | 4.9 | 33 | 11.9 | 236.8 | 17.5 | 3.8 |
| 10 | 12.1 | 244.4 | 18.3 | 3.9 | 21 | 13.5 | 264.6 | 16.3 | 4.2 | 34 | 12.7 | 246.4 | 17.1 | 4.2 |
| 11 | 12.4 | 249.2 | 18.0 | 3.8 | 22 | 13.4 | 255.9 | 17.3 | 4.3 | 35 | 12.6 | 240.0 | 23.8 | 4.1 |
| | | | | | 23 | 14.1 | 269.3 | 17.2 | 4.4 | 36 | 12.8 | 243.2 | 19.5 | 4.0 |
| | | | | | 24 | 13.3 | 259.4 | 15.8 | 4.5 | 37 | 12.6 | 239.4 | 19.5 | 4.2 |
| Average | 12.6 | 255.6 | 18.0 | 4.0 | Average | 13.6 | 259.0 | 16.9 | 4.3 | Average | 12.9 | 251.1 | 18.8 | 4.4 |

* The amounts of thiamine were calculated as thiamine hydrochloride.

When the cows were transferred from winter rations to pasture the volume of milk increased. Accordingly, one may question whether the cows maintained a steady output of ascorbic acid, riboflavin and thiamine, and the lower ascorbic acid and riboflavin contents of the milk were offset by the increased volume of milk. The average amount of milk produced daily during the three periods was 12.6 liters, 13.6 liters and 12.9 liters per cow. Thus the amount of milk per cow was greater during the early pasture period than it was when the cows were receiving winter rations. In the third period the volume of milk was less than it was during period 2 but slightly more than during the winter period. Hence the increase in the volume of milk more than compensated for the percentage decrease in the ascorbic acid content but did not compensate for the lower riboflavin content in the second period.

Inspection of table 2 reveals fairly uniform average total daily outputs of ascorbic acid, riboflavin and thiamine in the milk. The average

of the milk. Some Guernsey cows producing 4 liters of milk containing 16 mg. of ascorbic acid per liter had a total daily output of 64 mg., but other cows of the same breed producing 20 or more liters of milk containing 19.6 mg. per liter had a daily output of over 400 mg. of ascorbic acid. Similarily, Holstein cows produced about 4 liters of milk containing 19.2 mg. of ascorbic acid per liter, a daily output of 76 mg., but other cows of the same breed produced 21 or more liters of milk containing 17.4 mg. per liter, a daily output of 375 mg.

Practical dairymen generally believe that spring and early summer pastures provide a better ration for the dairy cow than the winter ration of food that has been stored for several months. In contrast to this opinion, the results

43. Holmes, A. D.; Tripp, F.; Woelffer, E. A., and Satterfield, G. H.: Relation of Volume of Daily Milk Production to Ascorbic Acid Content of Cow's Milk, Food Research **7**:111-117, 1942.

of this study show that early pasture is not superior to a properly produced, well selected winter ration and that pasture is likely to produce milk with a lower content of ascorbic acid and riboflavin than milk produced from a good winter ration. This conclusion is in agreement with the opinion of Hunt and Krauss,[39] who feel that milk obtained during the prepasture period is as high in riboflavin as that of the early pasture period, if not higher. It is also in agreement with the findings of Schwartze, Murphy and Hann,[22] who obtained a better quality of winter milk from ensilage-fed cows than any heretofore reported—almost, if not actually, as potent as the best summer milk obtained from cows on pasturage.

SUMMARY

This study was conducted to accumulate data concerning the influence of rations on the content of ascorbic acid, riboflavin and thiamine in cow's milk. It was confined to a consideration of the effect on a herd of 69 cows of the change from good winter rations to early pasture of rapidly growing green grass. When this change of ration was made, the content of ascorbic acid and of riboflavin in the milk decreased; but there was no change in the content of thiamine.

Mr. Eliot Greenwood and Prof. Clarence Parsons supplied the samples of milk and the information concerning the rations and management of the cows.

Massachusetts State College and Agricultural Experiment Station.

# Case Reports

## GANGLIONEUROMA OF THE BREAST IN A FIVE YEAR OLD CHILD

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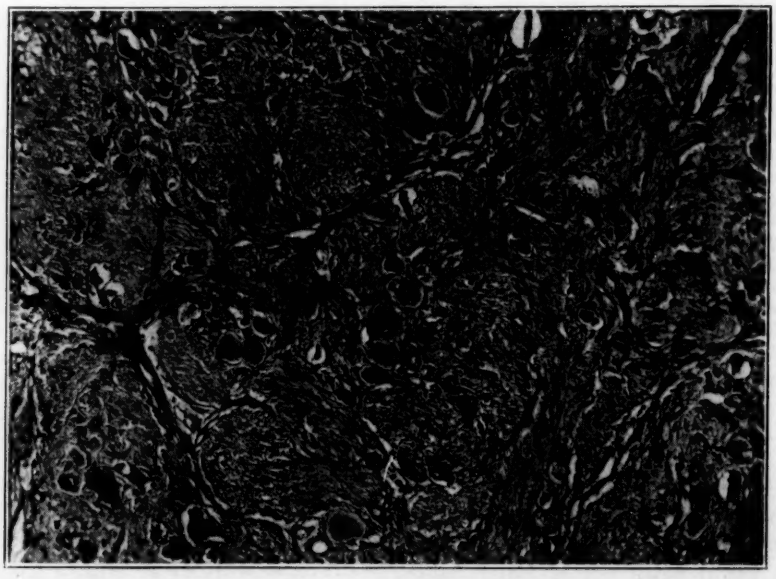
If tumors in the nervous system in adults are of great scientific interest, even more interesting are those occurring in children, in whom they are not so frequent. However, the study of tumors of the nervous system is discouraging because of the lack of clarity in the nomenclature, the confusion in the classification of the tumors and considerable doubt as to the treatment to be instigated in any specific case.

Ganglioneuroma, according to McFarland and Sappington,[1] who analyzed the 143 reports of cases appearing in the literature, is a rare type of tumor not only in children but in adults. Two of the 143 growths are listed as "thoracic," but, lacking the articles by Borst [2] and Guizetti [3] describing these, we do not know whether they were in adults or in children and whether or not they were located in the breast.

Ganglioneuroma of the breast can appear at any age; it is more frequent in women and girls than in men and boys and occurs slightly oftener on the left side than on the right. It may be simple or multiple, and when multiple the growths may be close together or widely distributed. The tumors vary from the size of a pea to that of a human head. The prognosis is excellent in cases in which tumors which are made up largely of mature cells are surgically extirpated; tumors of this type seldom recur.



Photomicrograph of a section of a ganglioneuroma from the breast of a 5 year old girl, showing the mass of intertwined nerve fibers with round and oval nerve cells distributed among them.

### REPORT OF A CASE

A 5 year old girl was brought to me because the mother had noticed a small lump in the breast which she believed had increased slightly in size during the previous six months, since she first became aware of it. No local pain or inflammation had ever been apparent.

The child was the only daughter of Portuguese parents. She had been breast fed for one year, and her

1. McFarland, J., and Sappington, S. W.: A Ganglioneuroma in the Neck of a Child, Am. J. Path. **11:** 429, 1935.

2. Borst: Demonstration eines wahren Neuroms, Berl. klin. Wchnschr. **34:**1063, 1897.

3. Guizetti, P.: Ganglioneuroma simysatico, Arch. per le sc. med. **55:**415, 1931.

nutrition was good. Occasional infections of the upper part of the respiratory system had been her only illness. There was no history of any injury, even minor, to the wall of the chest.

Physical examination showed that she was well nourished and of normal size for her age. The skin, mucous membranes and internal organs were normal. Palpation revealed a hard, movable nodule the size of a small walnut in the nipple of the left breast. There was no pain, inflammation or tenderness.

The tumor was excised with the area under local anesthesia, and the operation was followed by rapid cicatrization of the wound by first intention.

The pathologist, Dr. José Bica, reported the lesion as a hard, firm tumor which appeared cartilaginous. Microscopically, it was made up of neoplastic, adult nerve fibers which crossed each other in various directions. Along the severed fibers many round and oval nerve cells were distinguishable. On the basis of the microscopic structure the lesion was diagnosed as a ganglioneuroma of the breast.

Since, unfortunately, I was unable to follow this case I cannot report whether there was any recurrence or metastasis.

# BLEEDING PEPTIC ULCER IN INFANCY

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BALTIMORE

The problem of duodenal ulcers in children was first made known to the medical profession when, in 1901, Adriance [1] published a report of a case, including the clinical and postmortem observations. During the next few years data were accrued, in reports of autopsies and of cases indicating that the disease occurred more frequently than had been thought. Gerdine and Helmholz [2] found duodenal ulcers in 8 of 16 autopsies on "atrophic" infants. In 1913 Entz reported that 10 duodenal ulcers were observed in autopsies on 364 unselected infants under 1 year of age. In 1913 Holt [3] published a brilliant survey of the literature. Of the peptic ulcers reported in the series of cases analyzed by him, duodenal ulcers were most common. Of 65 patients 46, or 70 per cent, were between 6 weeks and 15 months of age; the condition occurred with the greatest frequency between the sixth and the tenth week. Holt emphasized that the age incidence corresponded to that of marasmus. Dickey [4] in 1926 pointed out that of 2,000 patients treated at the Mayo Clinic for peptic ulcer 42 had symptoms dating back to childhood. "This incidence of slightly more than 2 per cent points to the probable frequency with which chronic peptic ulcer in children is overlooked." Aside from sporadic reports of cases, no further review of the subject was published until Bird, Limper and Mayer's paper appeared in 1941.[5] They reported 243 cases in which 124 of the patients had been treated medically and 119 surgically. Of the total number of patients 68 (27 per cent) had bleeding ulcers, and of 54 infants under 1 year of age 25 (46 per cent) had bleeding peptic ulcers. Bird, Limper and Mayer found that most ulcers which occur in children under 2 months of age bleed or perforate, premonitory signs being minimal. In the older age groups the signs may be so manifest that the diagnosis is not too difficult if one bears in mind the possibility of such an occurrence. Ladd and Gross [6] observed a chronic duodenal ulcer in a 3 week old baby who died of another condition. It was their opinion that ulcers occur more frequently in infants than in older children.

## REPORT OF A CASE

A white girl 2½ months old was admitted to the pediatric service of Sinai Hospital on Aug. 13, 1943 because of vomiting which had persisted since she was 3 weeks of age. At that time the administration of solution of calcium hydroxide was started, which controlled the vomiting. During the next three weeks the child seemed to be entirely well and gained weight. The formula was changed, and orange juice was given. When cod liver oil was added to the diet the child began to have projectile vomiting which occurred about five minutes after the feeding. The vomitus consisted of milk and watery fluid and was never tinged with blood. There was no associated diarrhea; the stools were described as yellow, soft and never tarry or grossly bloody. At no time did the child appear to have any pain. At the time of admission to the hospital the infant appeared to be dehydrated and showed some signs of recent loss of weight, but she was not marantic. There were no other significant abnormalities. The hemogram showed 3,760,000 red cells and 6,650 white cells (of which 84 per cent were polymorphonuclear) per cubic millimeter and 12.5 Gm. of hemoglobin per hundred cubic centimeters (86 per cent). The urine contained 18 to 20 leukocytes and 6 to 8 erythrocytes per cubic millimeter; the albumin content was 2 plus, and there were no casts. The stools gave a weakly positive reaction with benzidine. The reaction to the flocculation test for syphilis was negative. A roentgenogram of the chest was normal, and cultures of material from the nasopharynx and from the nose and throat contained no pathogenic organisms. On

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‡ Resident Physician in the Medical Service at Sinai Hospital.
* Formerly Resident Physician in the Medical Service at Sinai Hospital; at present with the United States Public Health Service.

1. Adriance, V.: Duodenal Ulcer in an Infant of Ten Months, Arch. Pediat. **18**:277-279, 1901.

2. Gerdine, L., and Helmholz, H. F.: Duodenal Ulcer in Infancy in Infectious Disease, Am. J. Dis. Child. **10**:397-409 (Dec.) 1915.

3. Holt, L. E.: Duodenal Ulcers in Infancy, Am. J. Dis. Child. **6**:381-393 (Dec.) 1913.

4. Dickey, L. B.: Duodenal Ulcers in Children, Am. J. Dis. Child. **32**:872-877 (Dec.) 1926.

5. Bird, C. E.; Limper, M. A., and Mayer, J. M.: Surgery in Peptic Ulceration of Stomach and Duodenum in Infants and Children, Ann. Surg. **114**: 526-542 (Oct.) 1941.

6. Ladd, W. E., and Gross, R. E.: Abdominal Surgery in Infancy and Childhood, Philadelphia, W. B. Saunders Company, 1941.

August 14 the blood contained 85 mg. of urea per hundred cubic centimeters, and stools examined on the same day and on the following day reacted positively with benzidine. On August 16 the urea content of the blood was 47 mg. per hundred cubic centimeters. At this time sucking inspiratory movements developed, and the child appeared to be in severe respiratory distress. She was immediately placed in an oxygen therapy tent. Physical examination revealed a cyanotic, sallow child with normal heart and lungs. The edge of the liver was felt, 2 fingers below the costal margin, and the spleen and the left kidney were just palpable. Preceding this episode the infant had been receiving feedings through a stomach tube, and at the time of this crisis the tube was removed. The hemogram on this date showed 3,410,000 erythrocytes and 21,450 leukocytes (of which 72 per cent were polymorphonuclear) per cubic millimeter and 9.8 Gm. of hemoglobin per hundred cubic centimeters (68 per cent). The patient

The arrow points to the blood clot overlying the ulcer, which is situated just below the pyloroduodenal junction.

was afebrile, and a culture of urine taken on this date was later reported to be sterile. The next day the child was still afebrile, the cardiac rate was slow, the lungs were completely clear, the liver was palpable 3 fingers below the costal margin, and the right upper quadrant of the abdomen was slightly tender to palpation. The content of urea in the blood at this time was 27 mg. per hundred cubic centimeters, and the leukocyte count was 26,400, with 83 per cent polymorphonuclear cells. The child continued to be afebrile, but her cry became weak, and respiration was grunting. A convulsion occurred which left a transient rigidity in the left arm. Spinal fluid, obtained by lumbar puncture, was completely normal. In retrospect it seems probable that the convulsion may have been caused by a gastrointestinal spasm. The urine on this date contained white cells too numerous to count and an occasional red cell; the content of albumin was 2 plus. The erythrocyte count was 2.8 million; there were 7.8 Gm. of hemoglobin per hundred cubic centimeters (54 per cent), and the leukocyte count was 41,250, with 73 per cent of the cells polymorphonuclear. Severe toxicity of the cells was evident. On August 19 two successive cultures of material from the nasopharynx revealed type XXII pneumococci. Because of the continued drop in the level of hemoglobin, a transfusion of 100 cc. of whole blood was given into the tibia. On the same day signs of pneumonic consolidation were observed. The next day sudden acute respiratory difficulty developed; the child passed a large, grossly bloody stool and died. The clinical diagnosis at the time of death was azotemia, bleeding ulcer of either the duodenum or the stomach, congenital disease of the kidney and terminal bronchopneumonia.

Postmortem examination of the gastrointestinal tract revealed a normal esophagus and stomach. On the lateral duodenal wall, approximately 1 cm. distal to the pyloric ring, there was a firm, adherent, deep red blood clot, 0.8 cm. in diameter (fig.) The wall beneath the clot was so thinned by the deep ulceration that the color imparted by the blood clot could be seen easily from the serosal surface. Microscopic examination confirmed the depth of penetration of the ulcer. The entire small and large intestines were filled with a mixture of reddish brown fluid and blood clots. The lungs contained many palpably firm areas, which in sections were seen to be well defined areas of bronchopneumonia.

## COMMENT

Peptic ulcer is generally considered to be extremely uncommon in children. Holt [3] has made the observation that the age distributions of "marasmus" and of peptic ulcers are similar. It appears that a possible diagnosis of peptic ulcers is not considered in many cases, and in the vast majority of instances confirmation is difficult because of the lack of suggestive signs. Jankelson [7] speculated that the diagnosis is not made more frequently because "(1) Ulcer is not suspected in childhood. (2) In younger children a history cannot be obtained. (3) Uncomplicated cases do not give a history typical of ulcers. (4) Roentgen examinations of the digestive tract in childhood are not made with the same frequency as in adults."

Holt [3] emphasized that there is one definite symptom of duodenal ulcer, that is, hemorrhage. Of 64 patients with duodenal ulcers, 28 had bloody stools, 10 had bloody vomitus and 6 had both phenomena. Two patients had no discharge of blood during life, but at autopsy the intestines were found to contain clots. It was Holt's opinion that the loss of blood from the bowel may be so small as to give only a trace in the stools.

Other authors have indicated the association with peptic ulcer of pylorospasm of such severity

7. Jankelson, I. R.: Peptic Ulcers in Children, Am. J. Dis. Child. **44**:162-165 (July) 1932.

that in many instances the condition has been diagnosed as pyloric stenosis. Vomiting is present and may be projectile. As an aid in the differentiation, Reuben [8] emphasized that the age of onset of symptoms of ulcer is later than that of pyloric stenosis.

Wright [9] and Reuben,[8] on different occasions, noted that many infants with peptic ulcers have a peculiar, puppylike cry. At times some of these infants may cry as if they had colic.

It is possible that surgical intervention might have saved the life of this infant had the diagnosis been made earlier. Bird, Limper and Mayer [5] report in their survey an instance of perforated ulcer in a 2 day old infant in which surgical intervention was successful. We suggest that all infants who have projectile or persistent vomiting should be investigated roentgenologically.

Dr. Tobias Weinberg reported on the histologic sections and supplied the photograph.

8. Reuben, M. S.: Duodenal Ulcer in Infants: Report of Two Cases, Arch. Pediat. **51**:644-653 (Oct.) 1934.

9. Wright, H. P.: Duodenal Ulcer in Infancy with Report of Case, Arch. Pediat. **41**:646-653 (Sept.) 1924.

# PULMONARY HEMOSIDEROSIS IN A SIX YEAR OLD BOY

## A CLINICAL AND PATHOLOGIC REPORT

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Judging from a study of the literature, chronic interstitial pulmonary infiltration and hemosiderosis [1] must be rare in children and the diagnosis of this disease must be difficult to make while the patient is living. In the case here reported a diagnosis of chronic pulmonary infiltration was made from clinical and roentgenographic observation, and, although hemosiderosis was considered, after Anspach's report of a case of this condition [2] had been read, the patient presented such a different clinical picture that a diagnosis of hemosiderosis was not definitely made clinically.

The essential features of this report are as follows: An undernourished but otherwise normal 5 year old white boy passed through a period of a few months' duration, of rather severe anemia of unknown origin, associated with great fatigability and muscular weakness. Aside from this general condition, for some months the only positive sign was diffuse mottling of the pulmonary fields in the roentgenogram, suggesting chronic interstitial inflammation, which persisted until the death of the patient. About the sixth month of illness, when the child had recovered from the anemia, there was evidence of increased resistance to pulmonary circulation, breathlessness, clubbing of the fingers, and distinct enlargement of the pulmonary conus, evident clinically and roentgenologically, especially during a period of acute bronchitis. From this time until his death, about one and a half years from the onset of the illness, the general condition of the patient remained the same until gradual cardiac failure developed in association with an acute infection of the upper respiratory tract.

### REPORT OF A CASE

A 5 year old white boy entered the hospital July 3, 1939 because of weakness and anemia, which had begun about three months previously. The symptoms began gradually, with decrease in the boy's activity because of ready fatigue on exertion. He remained indoors and often, because of chilliness, preferred to be near a radiator. Early in April the family noted pallor of the skin, and the patient entered Lakewood Hospital,[3] where he received a blood transfusion for anemia (hypochromic). The transfusion improved the general condition of the patient for a time, but again in June he was given a transfusion, also with temporary improvement. At the time of the second transfusion a roentgenogram of the chest showed questionable pneumonia in the upper lobe of the right lung, which cleared considerably during the brief stay in the hospital. He had remained in bed for about two months previous to admission to City Hospital, at which time it was reported that he had had no cough or sputum in association with the present illness. His diet seemed satisfactory. His parents and 4 considerably older siblings were in normal health and there was no knowledge of any familial condition similar to that of the patient. Neither at this time nor later were any facts elicited in the history that gave a clue to the cause of the pathologic condition. As the essential features of this condition remained similar during the remainder of his life (one year), they will be summarized only; variations of importance will be noted as they arose.

On admission the boy was pale and slightly icteric. He was breathing rapidly but was not dyspneic; his pulse rate was rapid, even when he was resting in bed. The temperature varied from 37 to 38 C. (98.6 to 100.4 F.) during the month in which the patient was in the hospital. The child was of average height but much undernourished; his weight varied from 16 to 17 Kg. (35 to 37 pounds) during the year he was under observation, while the average weight for children 5 to 6 years old is 18.7 to 20.4 Kg. (41 to 45 pounds). There was a small retinal hemorrhage in the right eye, near the macula, which was absorbed later. At this time no abnormalities were noted in the respiratory or circulatory systems, except as already noted. The liver and spleen were never enlarged to palpation, except at the time of cardiac breakdown preceding death. The urine was not abnormal at this time or later. The reactions to the intracutaneous tuberculin test (amounts up to 1 mg.) and the Wassermann test were negative. The anemia was severe; the hemoglobin content of the blood was about 20 per cent. The numbers of red and white cells in the blood were 1,880,000 and 19,000 per cubic millimeter respectively, with the differential count not abnormal. There was severe hypochromia, microcytosis, anisocytosis and poikilocytosis; no regeneration was noted. Because of the severe anemia, transfusions of 200 cc. of citrated blood were given on July 4 and 8, before the studies of the blood were completed. Studies made after the transfusions, during the course of three weeks, showed that the platelets and reticulocytes were abundant, the red cells had returned to normal, the fragility (two tests) was similar to that of control subjects

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1. The term hemosiderosis is derived from the Greek "haima," blood, and "sideros," iron.

2. Anspach, W. E.: Pulmonary Hemosiderosis, Am. J. Roentgenol. **41**:592, 1939.

3. Dr. L. M. Starin and Dr. F. S. Cooper made available the notes from Lakewood Hospital.

(2 interns), the icteric index was 16 (normal 4 to 6) and the clotting time was normal (two minutes), but the bleeding time was a little prolonged (six minutes). When the patient was discharged from the hospital, one month after admission, the hemoglobin content was 70 per cent, there were 3,800,000 red cells and 16,000 white cells per cubic millimeter of blood, with a normal differential count and plenty of platelets and with reticulocytes still abundant.

A roentgenogram of the chest on admission disclosed an unusual condition, as seen in figure 1 *A*, a diffuse mottled infiltration, densest at the hili and radiating almost to the periphery, resembling miliary tuberculosis that had been flattened or squashed.[4] Because a similar picture had not been seen in proved miliary tuberculosis and because the reaction to tuberculin was negative, a diagnosis of miliary tuberculosis was not entertained nor was a diagnosis of leukemia or Hodgkin's disease thought to be tenable. An unusual form of chronic interstitial pneumonitis was thought possible. However, this condition usually follows one of the infectious diseases of childhood and is associated with an abundance of physical signs, and both history and signs were lacking in this patient. A lateral plate of the skull and of the femurs did not reveal abnormalities, except that the calvarium had the faintly moth-eaten appearance common in anemia. A film of the wrist when the boy was 5 years and 1 month old "shows the skeletal age when compared with Todd's standard to be approximately 5 years and 9 months." A sternal biopsy was reported as showing "hyperplasia of the leukocytic series." The patient left the hospital Aug. 2, 1940, with his general condition improved, the blood picture being essentially normal, except probably for a slightly increased icteric index, but the plates of the chest showed no appreciable change.

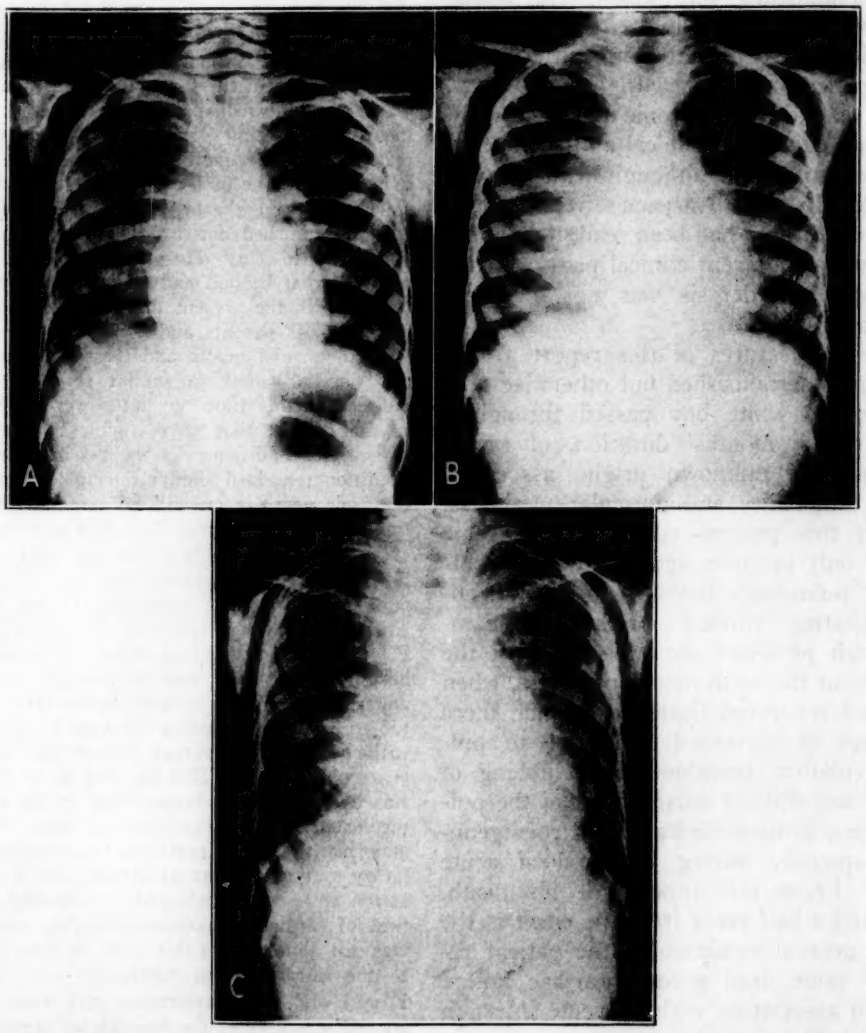


Fig. 1.—*A*, roentgenogram taken July 5, 1939. Note the diffuse mottling radiating from the hili. In the original film the infiltration can be seen to extend o the outer pulmonary fields. *B*, roentgenogram taken Sept. 13, 1939. Enlargement of the arc of the pulmonary artery is distinctly, seen. *C*, roentgenogram taken Aug. 5, 1940, twelve days before the death of the patient. Note the cardiac enlargement and the increased pulmonary infiltration, partly due to edema.

4. In the original film it was evident that the infiltration extended laterally with decreasing density to the periphery of the lungs. The reduced illustration, which does not show this, closely resembles the figures in Anspach's paper. It was the difference between the appearance of the full size plate and that of his illustrations that was confusing.

The patient was examined nine times, including an examination during a short period of hospitalization between the first and the final hospitalization. At each visit a general examination, with studies of the blood and urine and roentgenograms, was made. In September 1939 clubbing and cyanosis of the fingers and toes were noted. The number of erythrocytes per cubic millimeter of blood had increased to 5,000,000 and the hemoglobin to 90 per cent; there were 11,200 leukocytes per cubic millimeter, with an essentially normal differential count, and the icteric index was 24. The condition of the blood varied but little from normal at succeeding examinations; there were no further periods of anemia.

In October the patient was seen when convalescing from an infection of the upper respiratory tract with a moderate cough. Along with an increase in clubbing and cyanosis of the fingers, there was a striking increase in cardiac activity, especially in the visible and palpable impulse over the pulmonary conus, to the left of the sternum, accompanied by an extraordinarily loud and readily palpable closure of the pulmonary valve. Aside from this increased activity and slight enlargement to the right and over the pulmonary area, the heart seemed as before; the rate was 130 to 140. The systolic blood pressure was 105 mm. of mercury, with the diastolic pressure uncertain. There was also an increase in the anteroposterior diameter of the left side of the chest. The roentgenogram (fig. 1 *B*) showed a distinct increase in the size of the pulmonary conus but no particular increase in the pulmonary infiltration, as was expected from the physical signs. There were a few fine rales at the bases of both lungs at this time, the only time adventitious respiratory sounds were heard except during the period of cardiac failure preceding death. Even at rest the respiratory rate was as high as 60 per minute, without dyspnea however.

While the patient was in the hospital for a short time in the latter part of the same month, his general condition remained about the same. There seemed to be less air entering the right lung than the left, suggesting constriction of the bronchus by either a new growth or an enlarged lymph node. This change continued until his death, and autopsy showed that the pulmonary, bronchopulmonary and tracheobronchial nodes, especially those along the right primary bronchus, were much enlarged. At this time, too, the report on the roentgenogram of the thorax suggested the possibility of hemosiderosis of the lung. Clinically, this suggestion was not fully concurred in, because of the lack of physical signs and the complete lack of sputum, bloody or otherwise.

The patient's condition remained about the same through the winter and spring. There were no infections of the respiratory tract. The boy rested much of the time, but in fair weather he was outdoors, his activity greatly limited by shortness of breath, however. In July 1940, eleven months after the first time the patient was discharged from the hospital, there was not much increase in the pulmonary infiltration. Clinically, however, there was distinctly less cardiac reserve, with more obvious clubbing of the fingers, but the liver and spleen were not enlarged to palpation. There had been no change in the blood picture; the erythrocytes numbered about 5,000,000 per cubic millimeter, with the number of leukocytes also about normal. The conjunctivas were slightly icteric. One month later the child had an infection of the upper respiratory tract with increasing cardiac and respiratory embarrassment and cardiac dilatation (fig. 1 *C*). There were pronounced accentuation of the pulsation over the pulmonary conus, unusually loud closure of the valve and a faint apical systolic blow, considered to be due to cardiac dilatation.

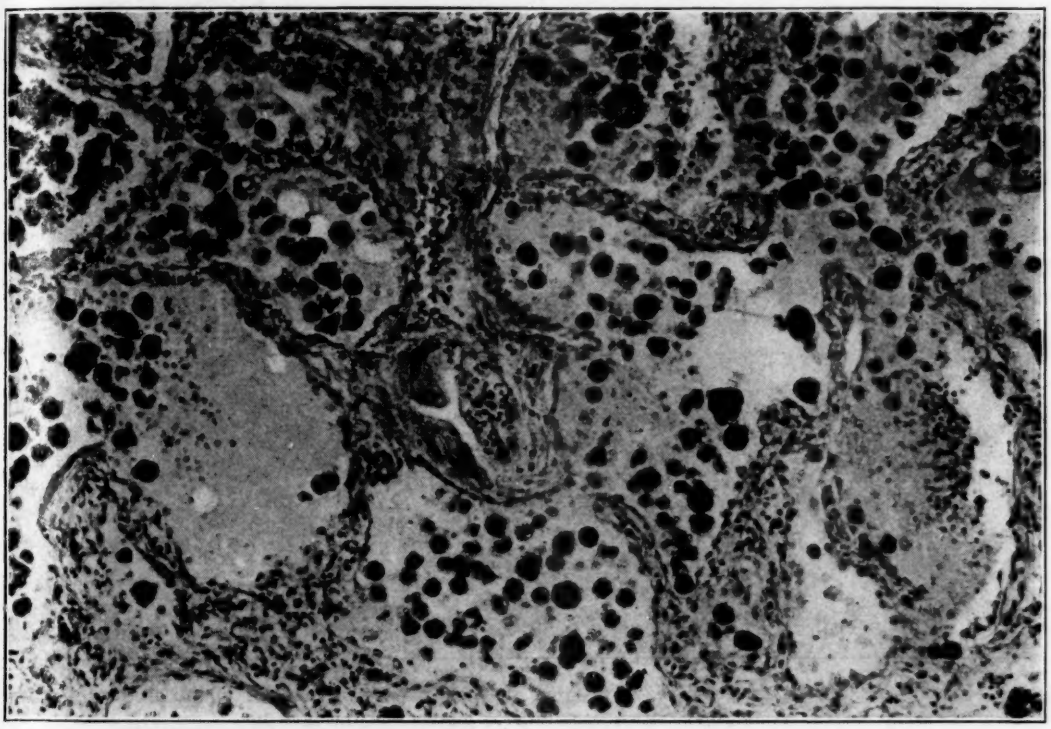

Fig. 2.—Section of lung (× 179; hematoxylin and eosin stain) showing hemosiderin-laden phagocytes within the alveoli. In the center is a siderotic nodule, with multinucleated giant cells containing pigmented filaments and hemosiderin.

The face was slightly puffy, but there was no other manifest edema. The abdominal wall resisted palpation for the liver and spleen. Auscultation over the lungs revealed no adventitious sounds. The family postponed hospitalization until four days later, when the patient was in a state of advanced cardiac decompensation with gallop rhythm, the details of which need not be given, except that by then the liver and spleen were much enlarged (liver down to the umbilicus). There was a little puffiness of the face but no appreciable edema of the extremities. Death occurred one week later. The cause was considered to be failure of the right side of the heart (cor pulmonale), secondary to chronic diffuse interstitial pulmonary infiltration of undetermined cause.

The autopsy was performed by Dr. David M. Earl, three hours after the death of the patient. The body was that of a poorly nourished, pallid white boy of 6 years, with moderate clubbing of the fingers. Bilateral hydrothorax (right side 300 cc. and left 100 cc. of fluid), hydropericardium (50 cc.) and ascites (300 cc.) were present. The heart was hypertrophic (150 Gm.—expected weight 94 Gm.) and dilated, especially the right ventricle. There was diffuse increase in the consistency of the lungs. Cross section revealed grayish brown mottled surfaces, with thickened interstitial septums. The tracheobronchial lymph nodes were moderately enlarged. Other organs were not unusual, grossly.

The pleura was thickened by fibrous connective tissue which contained evidence of recent focal hemorrhage and granules of golden brown pigment, both free in the tissue and in macrophages (fig. 2). Most of the alveolar spaces contained numerous macrophages filled with granules of golden brown pigment which varied greatly in size, the largest measuring approximately 15 microns. A few granules of pigment were free in the alveoli. There had been recent focal hemorrhage in the alveoli. Some macrophages contained well preserved erythrocytes. Many alveoli were lined by low cuboidal cells, which in some instances contained fine granules of brown pigment. The alveolar walls were diffusely but variably thickened by fibrous connective tissue containing many fibroblasts and fibrocytes, occasional macrophages, plasma cells, lymphocytes, neutrophilic polymorphonuclear leukocytes and multinucleated foreign body giant cells. Evidence of focal hemorrhage was also present. Granules of pigment, similar to those noted were present in the alveolar walls, both free and in macrophages. Yellowish green filaments, which proved to have the same color in the unstained sections, were seen in the alveolar walls, occasionally extending partially into alveolar spaces, some free and some completely or partially within giant cells. They occurred singly or in groups and were branched, septate or fragmented; some had bulbous ends. Capillary hyperemia was extensive. In some instances the capillaries were thickened and fibrotic, their walls occasionally containing circular lines of yellowish green pigment. The perivascular tissue was increased and resembled the tissue in the alveolar walls. Many perivascular lymphatic spaces contained pigment-bearing macrophages. A few of the small arteries and veins were thickened and contained yellowish green pigment, principally in the region of the internal and external elastic laminas (fig. 3). The larger arteries showed no such change, but in the adventitia there were fine granules of brown pigment. The bronchi and bronchioles were sparsely infiltrated with neutrophilic polymorphonuclear leukocytes and lymphocytes. In the walls of several bronchi were seen yellowish green filaments, already described as occurring in the alveolar walls. Within the bronchi were pigment-bearing macrophages.

An inferior tracheobronchial lymph node contained numerous macrophages and multinucleated giant cells of foreign body type in the peripheral sinuses and to a lesser extent in the central sinuses. These cells contained golden brown granules of pigment, and, in addition, many of the giant cells contained pigmented filaments like those seen in the lung. Some filaments also were free in the sinuses.

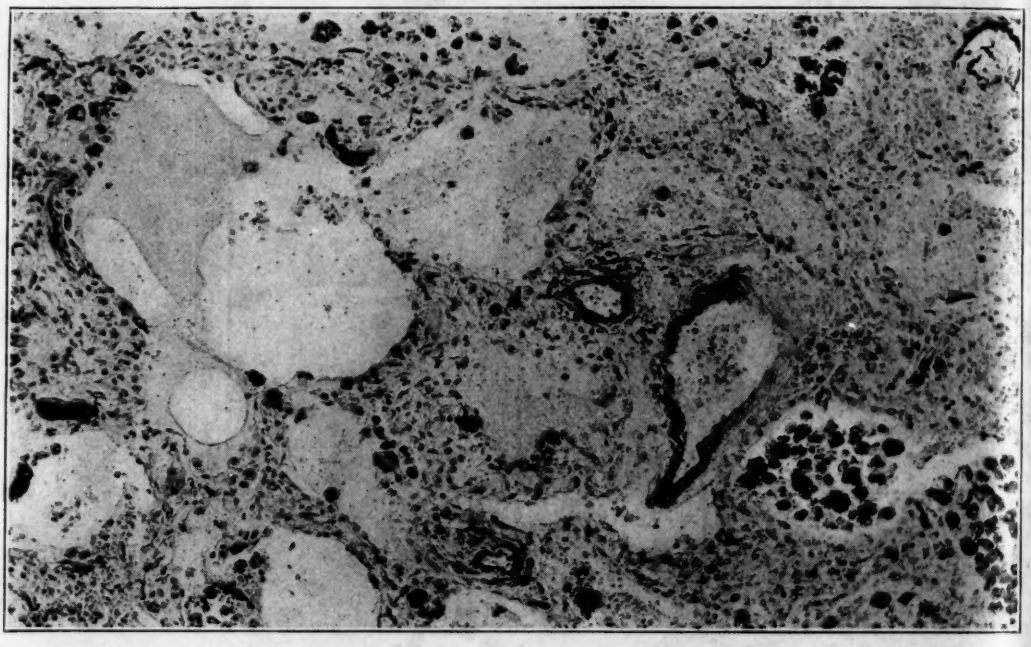

Fig. 3.—Section of lung (× 150, von Kossa's stain) showing masses of pigment in the alveolar septums and filaments in the walls of the vessels as well as hemosiderin pigment in the alveoli.

Special stains were used for sections from the lungs and lymph node: Van Gieson's, Heidenhain's azocarmine, Masson's trichrome stain, Wilder's stain for reticulin and Weigert's stain for elastic tissue. The connective tissue in the alveolar walls was stained by all except the elastic stain, which colored only a few fibers here and there. The capillaries which were thickened stained similarly. With Perles' test for iron some of the capillary walls, the elastic laminas of many small arteries and veins, the pigment granules and the pigmented filaments were blue. The filaments were yellowish green with the stain for reticulin, dirty yellow with Van Gieson's stain, pale blue with azocarmine and light to dark gray with von Kossa's stain; with purpurin (Grandis and Mainini), a stain for insoluble salts of calcium, they were yellowish brown. Weigert's stain for elastic tissue revealed some greatly thickened, frayed and fragmented elastic fibers in arteries and arterioles and stained some of the pigmented filaments light to dark gray. Examination of the fragmented fibers with a polarizing microscope revealed no particles within the tissue that could be interpreted as silica.

There was passive hyperemia but no pigmentation of the liver, spleen and kidneys.

## COMMENT

While Anspach's patient and the patient reported on here showed striking similarity in pathologic states, there were considerable differences as well as similarities in the clinical conditions. The similarities were the anemia, recurrent in Anspach's patient but recovered from by the patient herein described, dyspnea, and pulmonary infiltration, the last-mentioned symptom being the persistent manifestation in this patient, with accompanying circulatory changes. Anspach's patient had a frequent cough with bloody sputum, intestinal distention, frequently loose stools and occasionally gross or occult fecal blood, and the liver was enlarged months before death. None of these symptoms was present in the patient whose case is herein reported. The presence of latent tuberculosis in Anspach's patient was probably incidental.

The explanation of opacities in the films, according to Wells,[5] is that hemosiderin is one of the end products of the decomposition of hemoglobin from extravasated blood. It is hemosiderin that is radiopaque and forms the shadows in the roentgen plates. The cause of the hemorrhages into the pulmonary tissue in this patient is discussed in the next section.

The principal lesions in the lungs were diffuse fibrosis, capillary fibrosis, degeneration of elastic fibers of the alveolar septums, arterioles, small arteries and veins, pigmentation and focal hemorrhage. Since the hypertrophy of the heart was mainly right ventricular and there were no valvular lesions, it may be assumed that the pulmonary changes were primary. Neither the cause nor the pathogenesis of the disease could be established. Perhaps pulmonary fibrosis was the primary lesion. If so, it could have resulted in vascular lesions and hemorrhages, which were manifested clinically by cyanosis and dyspnea. Instances of severe embarrassment of pulmonary circulation have been noted in pulmonary fibrosis due to siderosis (Karsner[6]) as well as to other causes. The fibrosis in this case may have been of congenital origin, namely, a failure of regression of mesenchymal tissue, a change similar to that present in pneumonia alba. There was no evidence of syphilis in this instance, but Ammich[7] described 14 nonsyphilitic infants with diffuse pulmonary fibrosis. In none of his patients, however, was there pigmentation; moreover, none of the infants lived more than eleven months. On the other hand, the fibrosis may have been acquired. It may have been the result of a low grade inflammation in response to either an obscure infection or degeneration. Pneumonoconiosis was considered, but there was no clinical or pathologic evidence in its favor. The fibrosis might also be considered a progressive change, a hyperplasia of connective tissue. Histologic study gave no suggestion of neoplasia. In view of the fact that the patient was almost 5 years of age at the onset of the disease, it seems likely that this was an acquired rather than a congenital lesion. The inflammatory element was so small that it might have accompanied either an old retrogressive or a progressive change.

The possibility exists, also, that the vascular lesions were primary. The fibrosis of the capillaries may have been the end result of a retrogressive change which caused widespread hemorrhage, organization, fibrosis and pigmentation. No inflammatory exudate was present within any of the vessels. In Anspach's[2] patient there was hemorrhage and hemosiderosis as in ours, but there was also necrotizing arteritis, which was considered by him to be the cause of the hemorrhage. It cannot be established, either on a clinical or a pathologic basis, whether the fibrosis or the vascular lesion was primary. However, since there was no inflammatory exudate and no necrosis in the vessels, even at the site of recent hemorrhage, and since the vascular lesions might well have been secondary to vascular obstruction caused by fibrosis, it is probable that the diffuse fibrosis occurred first.

The pigmentation is not considered as a primary cause of this condition because hemosiderin

5. Wells, H. G.: Chemical Pathology, ed. 4, Philadelphia, W. B. Saunders Company, 1920.

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may be deposited in the lungs without fibrosis (Sheldon [8]) and because the formation of hemosiderin frequently follows hemorrhage, particularly if oxygen is readily available (Karsner [6]). Hemosiderin is relatively insoluble and is only slowly removed from the tissues (Wells [5]); hence there may be widespread deposition of the pigment throughout the lungs, even though the hemorrhage is focal.

The pigmented filaments (so-called siderotic nodules) found in the lungs of this patient resemble those in various organs which are seats of hemorrhage, stasis or necrosis. In some instances they contain iron and in others both iron and calcium. Kockel [9] described pigmented filaments, remarkably similar to those found in our patient, as early as 1889, in the lungs of a patient with pernicious anemia with chronic passive hyperemia. In his patient both calcium and iron were present. Bittrolff [10] described similar lesions, also containing iron and calcium, in the lungs of a patient with chronic passive hyperemia due to heart disease. Lubarsch and Plenge [11] described pulmonary incrustations of calcium and iron which were the seat of pulmonary tuberculosis. The most common site for pigmented filaments, however, is the spleen. Stengel [12] described them in the spleen of a person with splenic anemia associated with "atrophic cirrhosis" of the liver. Many others have since described lesions of this type in the spleen in a variety of clinical conditions. They have also been found in ovary (Schueppisser [13]), midbrain (Herzenberg [14]), retroperitoneal lymph nodes (Schueppisser [13]), hyperplastic thyroid tissue (Schueppisser [13]), liver and stomach (Moeschlin [15]) and in carcinomatous kidney (Morgan, Lieber and Stewart [16]). In some of the instances it could not be decided whether the pigment contained calcium as well as iron. At times von Kossa's stain was used to determine the presence of calcium, but Kraus [17] has shown that the results may be fallacious, since the pigment contains iron phosphate which also stains with silver nitrate. In tissues from our patient the von Kossa method gave a positive result, but the reaction to purpurin as a stain for calcium was negative.

There has been some dispute about the cause of these lesions. Jaffé and Hill,[18] as well as others, ascribed a parasitic basis for them, but Reimann and Kurotchkin [19] stated the belief that siderotic nodules in the spleen are not caused by fungi. More likely they are secondary to hemorrhage or to hemorrhage and necrosis, as indicated by Bennett,[20] or to stasis plus an unknown factor, as postulated by Bittrolff [10] and many others. The pigment is deposited on elastic and collagenous fibrous tissue according to Schueppisser [13] and Kockel,[9] particularly on degenerated elastic tissue. The filaments of pigment found in our patient are thought to be the result of incrustation of degenerated elastic fibers by blood pigment and are not considered to be related to the cause of the primary disease in the lungs.

SUMMARY

A white boy 5 years old, ill for about eighteen months, had severe anemia for the first six months and after recovery had progressive weakness, breathlessness and clubbing and cyanosis of the ends of the fingers. Roentgenograms showed diffuse fibrosis of the lungs and enlargement of the root of the pulmonary artery. Autopsy disclosed extensive fibrosis of the lungs, with great deposition of an iron-bearing pigment (hemosiderin) together with siderotic nodules, and also cardiac hypertrophy, especially manifest in the right ventricle. The cause of the condition was not determined.

3395 Scranton Road.
City Hospital.

8. Sheldon, J. H.: Haemochromatosis, New York, Oxford University Press, 1935.

9. Kockel, R.: Ueber die Kalkeisencrustation des Lungen-gewebes, Deutsches Arch. f. klin. Med. **64**:332, 1889.

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# Progress in Pediatrics

## POLIOMYELITIS

### II. RESULTS OF TREATMENT DURING THE ACUTE STAGES OF THE DISEASE

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Since 1922 all patients with infantile paralysis cared for in the Department of Contagious Diseases, City Hospital, Cleveland, by one of us and his staff have been treated according to the Toomey-Feiss method.[1] This method includes early active treatment, manipulation, massage, heating by infra-red rays, warm baths and other physical therapy. All of these procedures have been advocated separately or collectively by other authors. In addition, we have used no casts or fixed splints, although we have kept the patients in neutral positions by the use of sandbags and other devices. If the intercostal and diaphragmatic muscles were involved, a respirator was employed. This plan of therapy has been outlined previously by one of us (Toomey).[2] Some years prior to 1922 Feiss concluded that the lack of casts did not interfere with recovery.[3] Our subsequent experience in the treatment of over 1,600 patients in the acute stage of the disease has, in addition, convinced us that early active treatment has not harmed the patients. This paper reports the results in 226 patients treated by us during 1941 and 1942.

The objective of the Toomey-Feiss treatment has been to keep the muscles in good condition until the nerves regained their function. This is best done by keeping the involved areas well vascularized by the use of some form of heat, such as infra-red rays combined with warm baths. From the time the patient is admitted to the hospital, the muscles are moved through all their arcs of motion three to four times a day, or, if there is reflex tonic contraction, the contracted muscle is manipulated loose and the opponent stimulated with galvanic current, thereby being caused to contract.

The most important factor, however, is institution of physical therapy at the proper time and persistence in the use of this treatment. The parents of patients suffering from a severe attack of infantile paralysis must understand that the patient will be in the hospital at least a year, that physical therapy will have to be employed persistently during that time and that if they employ or insist on ambulatory treatment too early they may expect complications, substitution with contractions and scoliosis. Early treatment combined with physical therapy will give the patient extraordinary laxness of movement, but it is persistent, careful reeducation of muscles that brings about worth while results.

Misunderstandings arise as to results of therapy, usually because not all therapeutists speak the same language. Some of them group patients of all types together and treat them all, despite the fact that many patients need no treatment and recover without it. Obviously, statistics from clinics in which this method is employed might not reflect the actual results of a therapy, and percentages of recovery reported therefrom might be misleading.

In another communication[4] the basic considerations needed for judging therapeutic results in poliomyelitis were noted. A classification of patients with this disease was attempted. Nine groups were given, but it was found later that the classification could be contracted as follows:

Group 1. Patients with virus in the gastrointestinal tract.

(*A*) Without symptoms.

(*B*) With gastrointestinal symptoms (diarrhea, constipation, headache).

(*C*) With nausea and pain in the belly.

(Note: Even these three subdivisions might be grouped together.)

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1. We have referred to the method of physical therapy used as the Toomey-Feiss treatment. This descriptive term is used for convenience only, and not to imply that we have discovered a new form of physical therapy. All the modalities and methods of treatment employed have been occasionally used by others. What may be new is the fact that a form of early therapy has been consistently employed at City Hospital in Cleveland for at least twenty years and that enough data have been accumulated to give this way of treatment some standing in the care of infantile paralysis.

2. Toomey, J. A.: Treatment of Infantile Paralysis in the Acute Stage, Arch. Phys. Therapy **23**:650, 1942.

3. Feiss, H. O.; (*a*) The Treatment of Early Infantile Paralysis as Based on the Physiologic Indications, J. A. M. A. **78**:85 (Jan. 14) 1922; (*b*) Early Activation of Muscles in Infantile Paralysis, Ohio State M. J. **19**:177, 1923.

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Group 2. Patients with gastrointestinal symptoms plus significant changes in the spinal fluid but no paralysis.

Group 3. Patients with symptoms, especially gastrointestinal, and with signs of meningeal irritation, but no stiff neck and no paralysis.

Group 4. Patients with the same symptoms as those in group 3 plus a stiff neck.

Group 5. Patients with any or all of the signs already listed plus paresis or paralysis.

(*A*) With radicular paresis which is apparent only against severe force and which causes no functional impairment.

(*B*) With radicular segmental [5] paralysis not involving the phrenic and intercostal nerves.

(*C*) With radicular segmental paralysis involving the phrenic and intercostal nerves, with or without involvement of other somatic nerves.

(*D*) With bulbar involvement.

Alpha. Without radicular segmental spinal involvement.

Beta. With radicular segmental spinal involvements (sometimes including phrenic and intercostal nerves).

Gamma. With the seventh nerve involved solely.

(*E*) Alpha. With encephalitic plus bulbar or perhaps spinal involvement.

Beta. With encephalosegmental or encephalomyelitic types.

Gamma. With peripheral neuritis only or cortical involvement only (encephalitis or hemiplegia alone).

Delta. With Landry's disease (acute ascending myelitis).

Patients in groups 1 to 4 inclusive usually recover within the isolation period of twenty-one days and are discharged from the contagious disease hospital completely cured. Those in subdivision A of group 5 need but little more time to recover function completely, and they require scant physical therapy after discharge from the hospital. Years ago it was rare that patients other than those with paresis or paralysis of the trunk, legs or arms were admitted to a hospital. In communities in which the populace has become poliomyelitis conscious, many abortive, nonparalytic and slightly paretic attacks are now recognized. In our own experience they never constituted less than 20 per cent of the total number of attacks in epidemic years, and in some epidemics the percentage might rise to 35. The meningeal reactions, positive Kernig sign and stiff back and neck, now referred to as spasm of the hamstring, back and neck muscles, disappeared in the 43 patients (of the 226 in the whole series) who were in groups 3 and 4, so-called nonparalytic patients, in from two to twenty-two days; the average time was eleven days. The length of time that meningeal signs persist in poliomyelitis corresponds to the length of time that they persist in cerebrospinal meningitis. No one can claim that it is necessary to treat the symptoms of meningeal irritation; no one can claim that the recovery of patients with nonparalytic poliomyelitis with meningeal signs is due to any particular type of therapy.

Patients in group 5, who, in addition to signs of meningeal irritation, have paresis or paralysis, are those who require good physical therapy. A proportion of them will later need orthopedic care.

There is some discussion about the future condition of patients in subdivision A of group 5. Some persons go so far as to say that probably some earlier patients belonging to this group are now the children or adults with crooked backs and other asymmetric conditions due to unrecognized poliomyelitis. That weakness of the muscles of the back in patients with poliomyelitis may be unrecognized in a clinic is highly probable. There was 1 child in our series of 226 patients in whom weakness of the ham-

5. In the present and in a previous article by one of us [4] the term "segmental" has been used to distinguish central involvement in poliomyelitis from peripheral involvement in peripheral neuritis.

Anterior horn cells might be grouped as segregated aggregates serving as nuclei for groups of muscles, involvement of which would give a radicular or nuclear lesion. Thus, if there is paralysis of groups of muscles having the same radicular innervation, the lesion could be localized in the spinal cord and not at the periphery. "Radicular," however, is not a good term of designation, nor is "spotted" accurate, since it makes one think of multiple sclerosis.

The term "segmental" is loosely used by clinicians to denote roughly the levels of the cord involved in a disease.

McCouch, of the University of Pennsylvania, objects, and, correctly so, to the use of the word "segmental" in the present instance, since the term is wholly indefensible from a physiologist's viewpoint. Actually, all that one is justified in saying under the circumstances in question is that a lesion in the cord is present and that if it were lower motor neuron in character it could be localized in the cells of the anterior horn.

string muscles was found and demonstrated by the orthopedic surgeon some time after the admission of the patient to the hospital. The weakness, which was present all the time, was missed by us, although it had been noted by others, and only later revealed to us by the consultant in orthopedic surgery.

Group 5 must be subdivided, since paralysis of certain muscles causes distinctive and characteristic clinical reactions. Patients with isolated bulbar involvement are classified in group 5, subdivision D. These patients need no physical therapy, only postural drainage, mechanical aspiration and good nursing. They usually survive if they live for forty-eight hours after the onset of the illness. Patients with peripheral neuritis only, cortical involvement only or hemiplegia only respond to simple nursing likewise, although those with the last-named condition may need some physical therapy.

In a report on results, patients in groups 1, 2, 3 and 4 and in subdivisions D alpha and E gamma of groups 5 should be considered separately, since they may recover with a minimum of attention and thus, in the true sense, do not actually reflect the efficacy of any particular system or method of treatment.

What concerns the physician and the patient most is muscular paralysis. Therefore, actual beneficial effects of therapy must be demonstrated. In order that they may be demonstrated it is necessary to make extremely accurate comparisons as to the status of the muscles before and after treatment. Accordingly we have evolved a system of evaluation of the degree of involvement of muscles and extremities. In this classification we have arbitrarily set up a series of so-called "statuses," ranging from status I, in which no impairment of function of any muscle can be demonstrated, to status V, in which there is practically complete paralysis of all or most of the muscles. After the initial examination of the muscles is performed, soon after admission to the hospital, the patient is classified as being in one of these statuses. Just before discharge another comparable examination is made, and again the patient is rated.

These examinations consist of quantitative estimates, in terms of percentage, of the efficiency of function of individual muscles or groups of muscles. Thus, it can be readily ascertained whether or not, as a result of treatment, the patient has moved from a lower to a higher status. In this way the true beneficial effects of therapy, if present, can be seen at a glance.

Such an objective test is severe, but it teaches a sense of proportion, for it can be found that, according to the definitions, many patients in status V will remain there even after therapy. Such objective analysis as a final evaluation is too severe and does not give information as to the condition of the patient as a whole or as to the degree of betterment. The fact that a patient is still paralyzed and would still be classified as in status V does not signify that he is not better. This bare classification does not gage the passive results obtained by some workers. It does not indicate the ability to execute synchronous movements, even though the muscles are weak, nor does it indicate such factors as the degree of mobility, the absence of flail joints and the absence of deformity. Lay persons and sometimes physicians believe that the prime objective is to strengthen muscles. It is, to a certain extent, but the main objective is to keep muscles in balance. Persons with less than normal strength may walk synchronously and in rhythmic movement providing that all the muscles are equally strong and that they have sufficient strength to fix joints for locomotion and to bear weight. The muscles of a patient with pernicious anemia may be much weaker than those of some patients with poliomyelitis. However, the anemic patient walks synchronously, even though he may tire sooner than a normal person. A patient with poliomyelitis with 50 per cent of normal strength in an agonist muscle and 100 per cent in the antagonist muscle may well acquire deformities, despite the fact that he may be stronger than a patient with asthenic disease. Therefore, though a patient who recovers from poliomyelitis may not regain 100 per cent of normal muscular function, the muscles may be so balanced that synchronous movement is possible and, objectively, there is no difference in his gait. In brief, unless too much opposition is employed, a person may have weakness in groups of muscles both agonist and antagonist, and yet execute complicated movements with ease and skill. Such patients may be completely lax and their muscles passively movable in all arcs. They may have neither muscular contractions nor deformities. Such a picture denotes great improvement.

While it may be true that passive mobility in itself is of no direct aid to motion and that an easily movable set of muscles may be completely useless, on the other hand, it is known that mobility is a direct precursor of synchronous motion and that reflex tonic contraction of any extent prevents or hampers movement. Passive mobility may be of little use to the patient if the muscles remain completely paralyzed because of massive involvement of the motor cells of the cord. Under these conditions there is a question as to whether the muscles should be allowed to remain passively relaxed or whether in some instances the involved limbs should be fixed and

ankylosed or splinted in positions of greater mechanical advantage. This, however, is a subject for the orthopedic surgeon and not pertinent to this paper.

The patient should be examined on admission to the hospital and an estimation made of his muscular strength. When results of therapy are to be gaged, however, an estimate of the basic strength of the patient's muscles must be made at least two weeks after the onset of the disease, when edema has subsided. This should be done in order to avoid erroneous conclusions regarding patients who make a so-called spontaneous recovery. The status of the patient is compared subsequently at frequent intervals and at the time of discharge from the hospital. Such examinations do not harm the patient.

In addition to the ordinary estimation of muscular strength, the condition of muscles has also been graded objectively by Toomey and his staff for the past twenty years in terms of volts of galvanic current necessary to cause contraction. As physiologists state, the reaction to galvanic current parallels the normal contractile response of muscle. A greater number of volts must be applied to the motor point to cause the contraction of a muscle when there is some paresis or paralysis than when the patient has recovered muscular function. It should be noted, however, that as the patient improves the muscles may respond to a voltage which is considered a normal stimulation, i. e., the same amount of current which moves normal muscles may move the previously affected muscles, and yet the recovered muscles are not voluntarily movable. This response, nevertheless, is a good prognostic sign and means that the patient will soon recover voluntary motion. At the same time the patient who has been instructed to project impulses over his nerves will tell the physician that he feels that these impulses are traversing the nerve and that his muscles are moving long before they actually do. This, too, is significant and indicates the approach of voluntary movement.

Inasmuch as the response of muscles to galvanic current is not always constant or consistent, we have not used this method for evaluating the progress of our patients for purposes of this paper. Clinically, however, it has proved to be useful, especially as regards prognosis.

Following is an outline of our system of classification of patients according to the status of their muscular efficiency.

Status I. Patients in whom neither weakness nor paralysis is evident. They have normal passive mobility in all arcs. If a patient is found to be in this status after the course of treatment, he is regarded as 100 per cent cured.

Status II. Patients in whom there is a minimum of hidden weakness, detected only by careful examination against force. The muscular strength is approximately 70 to 90 per cent efficient, and there is complete passive mobility of all muscles. A patient in this status following treatment can be regarded as having a complete functional cure.

Status III. Patients who have slight paralysis in one extremity and perhaps severe paralysis in another. They may have paralysis in individual muscles, whether the disease is bulbar or spinal. The muscles involved are usually 40 to 60 per cent efficient. The patients have complete mobility of muscles and functional motility when they are supported by the observer or when braces are used.

Status IV. Patients who have severe paralysis of the muscles of two or more extremities. Function is limited, and muscular power is only 10 to 40 per cent efficient in the involved musculature.

Status V. Patients who are bedridden and have involvement of the muscles of all extremities and of other muscles as well, the efficiency ranging from 0 to 10 per cent.

Status VI. Patients who die.

Not all persons will progress from one status to another, even with treatment, but most patients will show obvious improvement within a status. For example, a patient in status IV may still have paralysis at the end of observation, but he may have functional ability, be passively mobile and have no contractures or flail joints. Or a patient may show improvement in one or more muscles or muscle groups but still have serious involvement of other muscles or of muscles in other extremities. Such a person has improved, nevertheless. Improvement within a status must be graded; for this purpose the patients in each status may be classified into three subdivisions according to their condition.

A. Patients who have shown minor improvement (from 10 to 20 per cent) in function and strength in some muscles and have passive mobility.

B. Patients who have shown great improvement (about 50 per cent) in function and strength in some muscles and have passive mobility.

C. Patients who have greatly improved function and strength in some muscles and have passive mobility without contractures but who still have obvious residual weakness at the end of a period of observation which prevents them from being considered as in a higher status.

This system of evaluating patients is unique in that it not only indicates the condition of the patient as a whole but takes into account minor improvements in individual muscles or muscle

groups as well as major progress in entire extremities or in the complete organism.

To illustrate our points, the classification of a patient on admission as 5B, status V, would indicate that he was bedridden and completely paralyzed. At discharge he might be classified as 5B, status V, condition C, indicating that though still bedridden he had made obvious and great improvement.

There are arbitrary ways of measuring improvement, such as estimation of the strength of the patient's muscles as a whole, of the muscles of an individual extremity, of a group of muscles or of an individual muscle. No method of estimation is altogether accurate, and probably the personal equation has at times entered into the calculations made by members of our house staff. Yet ratings made by one of us (Toomey), by his associates and by physical therapeutists have, surprisingly, been in agreement for the most part.

Early treatment will not cure every patient. The proponents of a treatment should not promise complete cure, for no method has ever been described that can accomplish this result in all patients, and no treatment can ever bring back destroyed motor cells.

It seems simple to formulate a set of rules and to make one's judgments fit each rule. Unfortunately, infantile paralysis is like any other disease. There are imponderables which must be considered when one speaks of therapy, for the very existence of some conditions accelerates and that of others militates against recovery.

In general, good results depend on (1) the length of time the patient is under the absolute control of the therapeutist, (2) the length of time the patient can be kept from using weak muscles contrary to and against gravity, (3) the age of the patient, (4) his intelligence and (5) his will to get well. Infants who recover sufficiently to climb around the crib may make substitutions which result in the development of deformities. Recovery is slow and difficult in the patient who does not understand what is wanted, in the lazy person and in the spoiled, pampered child. Adults who insist on walking too soon, despite adverse advice, those who demand their release in the midst of treatment and those who cannot be kept in bed and controlled because they are satisfied at the moment to use their muscles even though their movements are incorrectly executed are the patients in whom deformities may develop. Such deformities are the fault of the patient and not of the therapy. Despite all this, we have been severe in our estimations and have included all persons in our statistics regardless of their personalities, and, as stated before, we have estimated the results of our treatment on the basis of the conditions of the patients when they were discharged or passed from our control. In this respect we have ignored the imponderable. The patients considered are those who were kept in the hospital as long as it was deemed necessary. Included among these are 19 persons who, for various reasons, decided to try other forms of therapy elsewhere.

In the epidemic of 1941 there was an obvious increase in the number of patients with bulbar involvement. Sixty, or 26 per cent, of the 226 patients admitted to the hospital had this condition, which indicates an increase in the bulbar type of the disease. Forty, or two thirds of these, were 10 years or above in age. Only 5 (20 per cent) of the 25 in whom only the cranial nerves were involved died. Of the 35 with involvement of both cranial and peripheral nerves, 6, or 17 per cent, died. In all, 11, or 18 per cent, of the 60 patients with bulbar involvement died. Nine, or 22 per cent, of the deaths occurred among the 40 patients 10 years and above in age. Two, or 10 per cent, of the 20 patients below 10 years of age died. Thus the average in the two groups was about the same.

There were 226 patients in the entire series. Immediately 69 were declared unsuitable for the evolution of the results of treatment, 8 in group 3, 35 in group 4, 24 in group 5D alpha and 2 in 5E gamma. Most of these patients recovered completely before they were discharged from the hospital, in approximately twenty-one days. Our treatment need not have influenced the results in these patients. Some persons, using different methods, might claim that these 69 patients, constituting 30 per cent of our series, were cured by the methods employed.

Of the 157 patients to be considered, 19 in group 5B were in the hospital less than thirty days and left against our advice; they did not receive a full course of therapy. They left because they wished to have casts applied or for other reasons. Thus although 207 patients were treated, there were actually 138 in whom improvement might reflect results of therapy.

There was complete recovery in 29, or 21 per cent, of the 138 patients. If the 10 patients who recovered completely of the 24 in group 5D alpha were added, there would be 39, or 24.1 per cent, of 162 patients cured. For the 138 patients actually considered, the relationship of the status before treatment to the percentage of cures was as follows. Of the 12 patients in status II before treatment, 8 were cured (66.6 per cent). There were 82 patients whose status was rated III on admission; of these, 17, or 20.7

per cent, were completely cured. Of the 36 patients rated as in status IV on admission, 4, or 11.1 per cent, were cured. No cures were achieved among the 8 patients rated as in status V before treatment.

There were 27 patients, or 19.5 per cent of the 138 under consideration, who improved one status or more and could be classified as having good recoveries although they were not completely cured. These 27, added to the 29 completely cured patients, would make 56, or 40.5 per cent, who advanced from one status to the next or further.

Of the remaining 82 patients who did not progress one status or more, there were 10 (12.2 per cent) who improved to substatus A, 30 (36.6 per cent) to substatus B and 31 (37.8 per cent) to substatus C. None of those who lived failed to improve; 11, or 13.4 per cent, died. The total number of deaths was 17, or 7.5 per cent of the number of patients (226). If our data are analyzed by groups and statuses the following distribution is found:

In group 3, there were 8 patients in status I before and after treatment.

In group 4, there were 35 patients in status I before and after treatment.

In group 5A, there was 1 patient who was in status II before treatment and improved to status I, a complete cure.

In group 5B, there were 106 patients, but if we omit the 19 who were not given full treatment only 87 are left for consideration. Eleven of these patients were in status II before treatment; 7 improved to status I and 4 to status IIC. Fifty-eight were in status III before treatment; 11 improved to status I, 11 to status II, 5 to status IIIA, 14 to IIIB and 17 to status IIIC. Sixteen were in status IV before treatment; 2 improved to status I; 4 to status II, 2 to status III, 6 to status IVB and 2 to status IVC. Two patients were in status V before treatment; both improved to status VA.

There were 13 patients in group 5C. Three were in status III before treatment. One patient was cured or improved to status I; 2 died. Four patients were in status IV before treatment; 1 improved to status III, 1 to status IVB and 1 to status IVC; 1 died. There were 6 patients in status V before treatment; 2 improved to status IV and 3 to status VB; 1 died.

Group 5D alpha consisted of 24 patients. They were all in status III before treatment; 10 were cured or improved to status I, 1 to status II, 4 to status IIIB (?) and 4 to status IIIC; 5 died.

There were 35 patients in group 5D beta. Nineteen were in status III before treatment; 5 improved to status I, 4 to status II, 3 to status IIIB and 6 to status IIIC; 1 died. Of 16 patients in status IV before treatment, 2 improved to status I, 3 to status III, 2 to status IVA, 2 to status IVB and 1 to status IVC; 6 died.

There was only 1 patient in group 5D gamma. He was in status III before treatment and improved to status IIIA.

In group 5E beta was 1 patient in status III before treatment who improved to status IIIB.

There were 2 patients in group 5E gamma. One was in status I before and after treatment, and 1 died.

Nineteen patients in group 5B were released from the hospital less than thirty days after admission. On entrance, 11 of these were in status III. One did not improve; 9 improved to status IIIA and 1 to status IIIB. Six patients were in status IV on admission; 1 showed no improvement; 2 improved to status IVA and 3 to status IVB. Two patients were in status V on admission; 1 did not improve and 1 improved to status 5B.

Among the unrecovered patients was 1 with complete paralysis of the muscles of both legs who was taken away from us at the end of three weeks and placed in a cast. It was said that she was kept in this a few months, before her parents took her to Minneapolis, where far advanced flexion contractions and stiffness of the muscles of the back were found. This patient was given Sister Kenny's treatment at Minneapolis and had her muscles completely relaxed. Nevertheless, on discharge several months later she was still completely paralyzed. The patient, however, could be moved passively about through a complete normal arc of motion. Neither flailness nor deformities developed. The prognosis before she left our institution was that she would have complete paralysis.

From a critical analysis, it would seem that the percentage of recoveries was not so high as might be expected. It must be pointed out, however, that there are some factors not amenable to statistical analysis. Our patients, with 1 exception, were comfortable, a factor Feiss stressed in 1923.[2b] Except in the 1 patient, deformities did not develop and the muscles could be moved through the normal arcs of motion while the patients were under our care.

We cannot say that we have never had a failure, nor can we say that we never had a patient in whom a deformity subsequently developed. By the very nature of things this is impossible, for the exigencies of a particular case may force one to discontinue treatment. This was illustrated in a patient in whom there was involvement of the intercostal, diaphragmatic,

nuchal and laryngeal muscles as well as of the muscles of both arms and legs. Passive movements were unsuccessfully tried while the patient was in the respirator. Hot compresses were applied, and he nearly died. Manipulation was resorted to in desperation, but fixation progressed. Later, when we were able to take the patient out of the respirator, we returned to the use of infra-red ray therapy. We were not satisfied with the progress and felt that the Kenny method of treatment might give us better results. The reaction was severe, and the patient was made worse. The reasons are obvious. When the patient was covered with hot packs, there was an increase in the heart rate; he needed more oxygen and necessarily had to breathe faster. Consequently, the muscles, accessory and normal, which under ordinary circumstances could produce enough movement to expand the chest when the patient was quiet, now had to contract more often, thereby tiring him. He collapsed several times and had to be put back in the respirator. Finally, the patient and his family demanded that we discontinue the treatment. Despite this succession of events we felt that he should have the benefit of more hot packs. Later, when he was able to breathe without the respirator, we started the Kenny routine but again had to discontinue it as his stiffness became even worse. It is felt that such a result is not the fault of any treatment and that it would have occurred despite the use of any method.

When one of us (Toomey) began treating patients with poliomyelitis over twenty-two years ago, he was stimulated principally by the teachings of Feiss, though he could not accept all of Feiss's dictums, especially the one that all patients should be made to walk early. He felt that they should not walk unless they walked correctly, that is, synchronously and against gravity, without any limp and without any added jerky movement that would denote substitution of muscles. It was also his belief that patients should be kept in bed in a hospital, under the absolute control of some one who understood the treatment of infantile paralysis in its early stage. This is the time when these patients are problems for persons trained in physical therapy and interested in the early reeducation of muscles, whether they happen to be pediatricians, orthopedic surgeons or physical therapeutists. Ordinarily, a patient should not have orthopedic devices until and unless he has weak muscles and must get up and move against gravity. If he has weakness of muscles but enough muscular power to give him synchronous movement of a normal character, continued physical therapy is all that is necessary. If, however, the patient does not cooperate and there is a tendency to substitute and to limp, there is only one thing to do, and that is to have the orthopedic surgeon take charge and make some arrangements to protect the weakened muscle.

It is our prediction that the percentage of patients who will be referred to orthopedic surgeons in the future will be just about the same as in the past, but the patients will be in a better condition to profit by orthopedic aid.

Our results are as good as any previously reported. Hence, by inference, we could conclude that splints and fixed casts are not necessary during the acute stage of poliomyelitis and that early active treatment does not harm the patient.

It is felt that the secret of successful treatment is to keep the involved muscles in good condition by maintaining the vascular supply, with the aid of physical therapy, and to follow a program of reeducation of the muscles until such time as they can be used normally.

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# Abstracts from Current Literature

## Biochemistry; Bacteriology, and Pathology

CHEMOTHERAPY BY BLOCKING BACTERIAL NUTRIENTS: ANTISTREPTOCOCCAL ACTIVITY OF PANTOYLTAURINE. HENRY MCILWAIN and FRANK HAWKING, Lancet **1**:449 (April 10) 1943.

Many bacteria need for their growth small amounts of vitamin-like substances, and pathogenic organisms obtain some of these from their host. Pantoyltaurine is a compound which was designed to inhibit the growth of bacteria needing pantothenate, a substance of similar structure, by displacing it from the points at which it interacted with micro-organisms and so, in effect, starving them of a substance essential for growth. Hemolytic streptococci were particularly sensitive to this action in vitro, and their growth was retarded when the ratio of pantoyltaurine to pantothenate was above a certain range.

Pantoyltaurine was rapidly excreted by rats, but the ratio of pantoyltaurine to pantothenate concentrations in their blood could be kept above the range of the in vitro action for most of the day by frequent subcutaneous doses to which there was no intolerance. Rats so treated for four days were protected from approximately 10,000 lethal doses of a virulent strain of streptococci. Since the concentration of pantothenate in human blood is slightly less than that in the blood of the rat somewhat lower levels of pantoyltaurine would be adequate for therapeutic action in man.

LANGMANN, New York.

## Metabolism; Infant Feeding; Milk and Other Foods

TUBULAR REABSORPTION OF PHOSPHATE IN THE DOG. PAUL K. SMITH, ROBERT W. OLLAYOS and ALEXANDER W. WINKLER, J. Clin. Investigation **22**:143 (March) 1943.

Studies of the urinary clearance in dogs following the injection of isotonic solutions of neutral sodium phosphate, to attain high concentrations of serum inorganic phosphate, led to the conclusion that no limiting or "maximal" rate of tubular reabsorption of inorganic phosphate could be demonstrated and that the relation of the excretion of phosphate to its concentration in serum and to glomerular filtration is similar in character to the relation of sulfate and potassium.

GUEST, Cincinnati.

URINARY EXCRETION AND SERUM CONCENTRATION OF INORGANIC PHOSPHATE IN MAN. ROBERT W. OLLAYOS and ALEXANDER W. WINKLER, J. Clin. Investigation **22**:147 (March) 1943.

Data on the changes in concentration of inorganic phosphorus in the serum and the rate of excretion of phosphate in the urine of normal and of diabetic human subjects during varying periods after fasting, after eating and after receiving insulin or intravenous infusions of sodium phosphate led to the following conclusions: (1) The rate of urinary excretion of phosphorus by man normally does not depend primarily on the concentration of phosphorus in the serum, although it may be influenced by changes in the latter; (2) following the intravenous injection of large amounts of neutral isotonic solution of sodium phosphate in normal man, the rate of urinary excretion of phosphorus is mainly determined by the concentration of phosphorus in the serum, and (3) injected phosphate is distributed through a greater volume than that of the extracellular fluid.

GUEST, Cincinnati.

AMINO ACID STUDIES: II. PLASMA AMINO ACID RETENTION, AS EVIDENCE OF IMPAIRED LIVER FUNCTION; INVESTIGATIONS IN CHILDREN WITH NEPHROSIS AND LIVER DISEASE. J. D. LYTTLE, E. GOETTSCH, D. M. GREELEY, W. M. GRIM and P. DUNBAR, J. Clin. Investigation **22**:169 (March) 1943.

Studies were made on the reactions to intravenous injections of casein hydrolysate and the rate at which this substance was metabolized, by measurements of the amino acid nitrogen of the plasma and of the urinary excretion of nitrogen after such injections in normal children and in children with nephrosis, nephritis or hepatic disease. In 45 children who were patients in a hospital but who had no impairment of renal or hepatic function, the fasting level of the amino acid nitrogen in the plasma ranged from 2.92 to 4.63 mg. per hundred cubic centimeters.

After intravenous injection of casein hydrolysate a delay in clearing the plasma of amino acids as compared with the rate of clearance in normal children was observed in 4 children with portal cirrhosis; in 2 of 7 patients with hepatic disease other than cirrhosis a moderate delay was noted. In 1 patient with hepatosplenomegaly and impaired renal function retention of plasma amino acid was noted, which disappeared when the enlargement of the liver and spleen abated. On the other hand, patients with nephrosis, chronic glomerular nephritis and other types of renal disease cleared the plasma of amino acids as quickly as the normal controls.

The rate of excretion of ammonia in normal controls and in patients with nephrosis was doubled immediately after the injection. In 5 patients with severe impairment of renal function, no increase in the rate of excretion of ammonia was noted.

GUEST, Cincinnati.

NITROGEN STORAGE FOLLOWING INTRAVENOUS AND ORAL ADMINISTRATION OF CASEIN HYDROLYSATE TO INFANTS WITH ACUTE GASTROINTESTINAL DISTURBANCE. ALFRED T. SHOHL, J. Clin. Investigation **22**:257 (March) 1943.

Data are reported on the nitrogen intake, output and balance of 20 infants, 2 weeks to 8 months of age, with gastrointestinal disturbances with and without demonstrated infection but not including children with infections such as dysentery or typhoid. The infants, with vomiting, diarrhea, dehydration and acidosis, were able to retain nitrogen when it was given in adequate amounts in the form of a casein hydrolysate intravenously or orally or by both routes. Positive nitrogen balances were obtained when the nitrogen intake was

0.35 Gm. per kilogram per day. Retention was greater when the nitrogen intake was greater, and in some infants with gastrointestinal disturbances the degree of retention was as great as that reported for well infants. Retention was greater, both in amount and in proportion to intake, when blood transfusions were given in conjunction with casein hydrolysate therapy.

GUEST, Cincinnati.

INFLUENCE OF LECITHIN FEEDING ON FAT AND VITAMIN A ABSORPTION IN MAN. DAVID ADLERSBERG and HARRY SOBOTKA, J. Nutrition **25**:255 (March) 1943.

Adlersberg and Sobotka adopted a modification of Nissen's test for fat and vitamin A tolerance as standard procedure in a study of intestinal absorption in patients with sprue and in normal persons. Active sprue is characterized by absence of the usual elevation of the total lipids or of the vitamin A content of the serum after a test dose of fat or of vitamin A. The addition of lecithin enhanced the elevation of the total lipid and vitamin A content of the serum. Lecithin (according to these investigators) apparently increases absorption and perhaps to a lesser extent mobilizes the hepatic deposits.

FREDEEN, Kansas City, Mo.

NUTRITIVE ADEQUACY OF CERTAIN LOW-COST FOOD MIXTURES. FRANCES HEMPHILL, RUTH ADELE KOENIG and JET WINTERS, J. Nutrition **25**:285 (March) 1943.

In an effort to establish a combination of very cheap foods that might be used as a basis for the dietary in low income groups, the authors calculated four adequate food combinations and assayed them for certain vitamins and minerals. Growth in rats on these diets was used as a further test of adequacy. "Two of the low-cost food mixtures were similar to the higher priced diets in vitamin and mineral content and in the growth response produced in animals."

FREDEEN, Kansas City, Mo.

DIGESTIBILITY OF SOME ANIMAL AND VEGETABLE FATS. RALPH HOAGLAND and GEORGE G. SNIDER, J. Nutrition **25**:295 (March) 1943.

The digestive coefficients of several animal and vegetable fats were determined by experiments with young male albino rats. Each fat was incorporated in an otherwise adequate diet in the proportions of 5 and 15 per cent by weight, corresponding to 12.5 and 32.7 per cent of the total caloric values of the diets. The following digestive coefficients were obtained when the diets contained 5 and 15 per cent fat respectively: coconut oil 98.9 and 96.5 per cent, soybean oil 98.5 and 98.3 per cent, corn oil 97.5 and 98.3 per cent, butterfat 88.3 and 90.7 per cent, mutton tallow 74.6 and 84.8 per cent, oleo stock 74 and 86.7 per cent and cacao butter 63.3 and 81.6 per cent. Hoagland and Snider stated that there was no consistent relationship between the melting points of the fats and their digestive coefficients.

FREDEEN, Kansas City, Mo.

FAT EXCRETION BY NORMAL CHILDREN. HAROLD H. WILLIAMS, ELIZABETH N. ENDICOTT, MARION L. SHEPHERD, HARRY GALBRAITH and ICIE G. MACY, J. Nutrition **25**:379 (April) 1943.

The excretion of fat of 19 healthy children (4 to 12 years) was investigated during five hundred and thirteen periods of five days each while the subjects were on diets of high nutritive quality. The intakes of fat varied from 62 to 113 Gm. per day and the utilization from 96 to 98 per cent. The amounts of free fatty acids, neutral fat and unsaponifiable material excreted were approximately equal for all the children, but the amount of soap excreted was higher for those on diets higher in fat. The soaps comprised about 50 per cent of the total fecal fat; unsaponifiable fat, 30 per cent, and free fatty acid and neutral fat, about 20 per cent each.

FREDEEN, Kansas City, Mo.

FURTHER INVESTIGATIONS ON PRESENCE OF RH ANTIBODIES IN BREAST MILK. ERNEST WITEBSKY and ANNE HEIDE, Proc. Soc. Exper. Biol. & Med. **52**: 280 (April) 1943.

Rh. antibodies were demonstrated in the colostrum and breast milk (fifth day), in titers of 1:8 and 1:16 respectively, from 2 mothers who delivered infants with erythroblastosis fetalis.

HANSEN, Minneapolis.

ENDEMIC FLUOROSIS IN GREAT BRITAIN. LEO SPIRA, Edinburgh M. J. **50**:237 (April) 1943.

Spira reviews the early demonstrations of the endemic nature of chronic fluorine poisoning in Britain, beginning in 1928. He has contributed numerous articles on this subject to the British literature.

The author states that the widespread endemic distribution of fluorosis in England is indicated by the occurrence of mottled teeth and of dystrophies of other organs. Fluorine enters the drinking water from such mediums as filter powders used in the process of purification of water, from the material, such as concrete, employed in the building of wells and storage tanks, and from various pipes and tanks made of iron. He discredits the theory that the fluorine comes largely from the soil; a sample of chalk containing little fluorine before going into the tank showed as much as 2.4 parts per million when taken from the tank water. Both fluorine and arsenic occur frequently as impurities in minerals and in metals.

NEFF, Kansas City, Mo.

THE CLEANSING AND STERILIZATION OF MILK BOTTLES. BETTY C. HOBBS and G. S. WILSON, J. Hyg. **43**:96 (April) 1943.

Hobbs reports an extensive and detailed study of the handling of milk bottles in Greater London, extending from October 1937 to July 1939. Two hundred and four visits were made to 105 plants of twenty-six different types, and 2,406 bottles were taken for sampling.

The general conclusion was that as good results may be obtained in large or small rotary plants relying on sterilization by a caustic detergent as in plants employing steam sterilization, and that the uniformly best results are obtained with properly designed and operated equipment of the spray type. Bottles emerging from the detergent section (sodium hydroxide with added trisodium phosphate or similar substance) of a properly operated plant are virtually sterile. In nearly all types of plants they became recontaminated during the subsequent rinsing. Contaminated, recirculated rinse water is the great danger. To correct this, the authors favor the use of a hot spray with a temperature too high for bacterial growth, to replace the warm recirculated rinse water. They feel that this is superior to the use of a chlorine compound, a method widely favored in the United States. Details of avoiding contamination of the bottles before refilling are also given.

JANNEY, Wauwatosa, Wis.

THE IMPORTANCE OF BREAST FEEDING. CHARLES MCNEIL, Practitioner **150**:193 (April) 1943.

The author lists as the advantages of breast feeding the following: (1) It supplies complete food and fluids for the first six or nine months of life; (2) supplies food at the right temperature and with the minimum chance of bacterial infection; (3) breast-fed babies are less susceptible to other types of infection of the alimentary or respiratory tract and to nutritional diseases; (4) suckling is a stimulus to maternal involution. He also discusses the reasons for the decline of breast feeding, the early difficulties and the reasons for the disappearance of breast milk under ordinary circumstances.

The article should be read in its entirety by those interested in breast feeding.

THELANDER, San Francisco.

A MILK POLICY FOR CHILDREN. WILLIAM SAVAGE, Practitioner **150**:199 (April) 1943.

The author in this paper reviews the necessity for greater amounts of milk for children and the processes by which that milk can be rendered safe. He discusses both bovine and human tuberculosis.

THELANDER, San Francisco.

## Vitamins; Avitaminoses

VITELLIN, CASEIN, LIVER AND MUSCLE TISSUE AS SOURCES OF PHOSPHORUS FOR THE RACHITIC RAT. RUDOLF BUNKFELDT and HARRY STEENBOCK, J. Nutrition **25**:309 (April) 1943.

Bunkfeldt and Steenbock found that the phosphorus of ovovitellin was present in a different form from that occurring in casein. It took more than twice as much vitellin phosphorus as inorganic phosphorus, at a calcium-phosphorus ratio of 3:1, to produce the same degree of calcification of bone in the rachitic rat, while the phosphorus in casein was equal in value to inorganic phosphorus. The phosphorus in muscle (pork loin) was definitely less available than inorganic phosphorus, but not to the same degree as vitellin phosphorus. Ovophospholipid phosphorus and the phosphorus in pork liver approximated inorganic phosphorus in value.

FREDEEN, Kansas City, Mo.

THE AVAILABILITY FOR HUMAN NUTRITION OF THE VITAMIN C IN RAW CABBAGE AND HOME-CANNED TOMATO JUICE. MARY M. CLAYTON and RUBY A. BORDEN, J. Nutrition **25**:349 (April) 1943.

Clayton and Borden, on the basis of analyses of both blood and urine, state that vitamin C from both raw cabbage and tomato juice was utilized by four young adults as well as or possibly better than that from pure vitamin tablets. An average of 116 Gm. of cabbage or 208 cc. of tomato juice provided 50 mg. of vitamin C.

FREDEEN, Kansas City, Mo.

OBSERVATIONS ON INDUCED RIBOFLAVIN DEFICIENCY AND THE RIBOFLAVIN REQUIREMENT OF MAN. RAY D. WILLIAMS, HAROLD L. MASON, PAUL L. CUSICK and RUSSELL M. WILDER, J. Nutrition **25**:361 (April) 1943.

The authors found that man needed an intake of 0.5 mg. of riboflavin per thousand calories to approximate the minimal daily requirement for the maintenance of satisfactory stores of riboflavin in the tissues.

FREDEEN, Kansas City, Mo.

MINIMUM VITAMIN A REQUIREMENTS IN INFANTS AS DETERMINED BY VITAMIN A CONCENTRATION IN BLOOD. J. M. LEWIS and OSCAR BODANSKY, Proc. Soc. Exper. Biol. & Med. **52**:265 (April) 1943.

Twelve infants with subnormal levels of vitamin A in the blood, due to the use of diets devoid of that vitamin, were given daily supplements of 150, 600 and 1,200 U. S. P. units as cod liver oil U. S. P. After four weeks the blood levels for vitamin A were again determined. The infants receiving the lesser amounts were found to have no appreciable change in the vitamin A levels, whereas those receiving 1,200 units daily now had levels in the normal range. In one infant who received 600 units daily the blood level, which had been 48 units per hundred cubic centimeters, dropped to 32 units at the end of four weeks. These studies indicate that for infants under 7 months of age the minimum requirement for vitamin A is between 600 and 1,200 units, or 100 to 200 units per kilogram, per day. This method of determination indicates a vitamin A requirement by infants four times and probably eight times as great as the requirement established on the basis of the dark adaptation method.

HANSEN, Minneapolis.

VITAMIN C SATURATION TEST. LESLIE J. HARRIS, Lancet **1**:515 (April 24) 1943.

Groups of boys (12 to 36 in each group) at a residential home were kept on a basal diet with a known content of vitamin C and given, in addition, various graded supplements of vitamin C, natural and synthetic, over periods of three or four months or longer, so that each boy in a group received the same amount. About twice a year (an interval found to be long enough to allow the effect of any previous saturation test to become negligible) the boys were tested by a standardized procedure previously described; 700 mg. of ascorbic acid per 10 stone (63.5 Kg.) of body weight was given daily, and the number of days were counted until the approach of saturation (taken as an excretion of 50 mg. or more per 10 stone in a two and a quarter hour specimen collected at the peak of excretion, about the fourth or fifth hour after each test dose). Daily intakes of 75, 60, 50 and 45 mg. gave responses of decreasing magnitude on the first day; 37 mg. produced responses on the first or second day and 23 mg. on the second or third day.

As a standard for use in assessing results of surveys, it is noted that the League of Nations requirement (30 mg. a day) or an amount not seriously in excess of it suffices in virtually all subjects to give responses by the second day of dosing. The use of the saturation test does not necessarily indicate a presupposition that saturation is physiologically desirable. "Substandard" is not synonymous with "clinically deficient," and there are degrees of partial deficiency between optimum nutrition and frank avitaminosis.

LANGMANN, New York.

## Hygiene; Growth and Nutrition; Public Health

ASSISTANCE TO THE ABANDONED AND DELINQUENT CHILD SHOULD BE INTEGRATEDLY TECHNICAL. PEDRO RUEDA, Bol. Inst. internac. am. de protec. a la infancia **16**:455 (April) 1943.

The author emphasizes that agencies involved in the care of the abandoned child should be economically independent and not under political domination. A competent personnel and facilities for adequate teach-

ing must be available. The physician and judge should cooperate in giving advice for the treatment and training of abandoned and delinquent minors. The national government of Argentina should assume responsibility for supervision of all agencies involved.

LESLIE, Evanston, Ill.

SCHOOL ATTENDANCE AND CHILD LABOR IN THE UNITED STATES. GERTRUDE FOLKS ZIMAND, Bol. Inst. internac. am. de protec. a la infancia **16**:480 (April) 1943.

The author first discusses educational progress in the United States. The movement for tax-supported schools did not make much headway until the beginning of the nineteenth century, and not until 1852 was the first general compulsory attendance law passed, in Massachusetts. Since then, although the different states vary considerably, there has been a remarkable increase in the percentage of the population 5 to 17 years of age enrolled in public elementary and secondary schools. Tables are given showing attendance according to age groups, rural and urban areas and nativity. There is also a table of states ranking poorest in educational programs.

Child labor likewise varies in different states, although there is a minimum age (16 years) for employment in all industries which produce goods destined for shipment in interstate commerce. This regulation does not apply to agriculture, in which child labor is extensive. There is pending, however, a bill setting a 16 year age minimum for such work during school hours and a 14 year age minimum for such work outside school hours on crops to be shipped in interstate commerce.

In the last part of the article the author discusses the effect of war production on child labor and school attendance. The legal employment of children is increasing, but also many instances of illegal employment have been noted. High school enrolment has dropped. The necessity of guarding the education and the wholesome development of the youth of the country has been emphasized by the Commission of Children in War Time. "No boy or girl shall be employed at wages that undermine wages for adult labor; none under 14 years of age shall be a part of the labor force; none under 16 shall be employed in manufacturing and mining occupations; none under 18 in hazardous occupations."

LESLIE, Evanston, Ill.

TEN YEARS OF CHILD WELFARE WORK IN URUGUAY. VÍCTOR ESCARDÓ Y ANAYA, Bol. Inst. internac. am. de protec. a la infancia **16**:524 (April) 1943.

On the occasion of the retirement of Dr. Roberto Berro from the Children's Council, the author reviews the actions carried out in Uruguay in child welfare work for the last ten years, the period in which Dr. Berro was at the head of the establishment. The activities of the council in that period began with the promulgation of the children's code which coordinated Uruguayan legislation in relation to childhood and established a unique agency, the Children's Council, to act in behalf of minors. At the same time the juvenile court was established, to act in place of parents. Protection during early childhood, later childhood and adolescence was completely reorganized and improved.

FROM THE EDITOR'S SUMMARY.

## Prematurity and Congenital Deformities

CONGENITAL ANEURYSMAL DILATATION OF THE AORTA ASSOCIATED WITH ARACHNODACTYLY. R. W. BAER, H. B. TAUSSIG and E. H. OPPENHEIMER, Bull. Johns Hopkins Hosp. **72**:309 (June) 1943.

The occurrence of cardiac enlargement and aneurysmal dilatation of the ascending arch of the aorta is reported in 2 cases of arachnodactyly. The aneurysmal dilatation appeared to be due to a congenital malformation of the tunica media. AUTHORS' SUMMARY.

THE EXCRETION OF KETOSTEROIDS IN HUMAN PREGNANCY URINE IN RELATION TO THE SEX OF THE FOETUS. H. BURROWS, DOUGLAS MACLEOD and F. LLOYD WARREN, J. Obst. & Gynec. Brit. Emp. **50**: 212 (June) 1943.

Certain observations have seemed to show that in embryos the androgenic cells of the male gonad begin to secrete before the ovary has become completely differentiated and that the ovary does not produce secretion until a much later stage of development.

For this reason the authors examined the urine of women during the early period of gestation to discover whether the testes of the male embryo might produce enough androgen to cause a recognizable increase of androgen in the mother's urine. They found that, while pregnancies in which there were especially high urinary concentrations of ketosteroid terminated in the birth of a male child, in general no significant difference was found between urine from pregnant women bearing a male fetus and those bearing a female fetus.

CUMMINGS, Evanston, Ill.

## Newborn

THE OCCURRENCE OF ABNORMAL CAPILLARY FRAGILITY IN THE NEWBORN. WILLIAM CURRY MOLONEY, Am. J. M. Sc. **205**:229 (Feb.) 1943.

In a preliminary study of capillary resistance 33 of 55 newborn infants (60 per cent) showed more or less abnormal capillary fragility.

This decreased capillary resistance disappeared as the infants became older.

Various factors influencing permeability of the capillary wall are outlined, and the possible relationship of abnormal capillary resistance to hemorrhagic disorders in the newborn is postulated. HENSKE, Omaha.

FETAL DISTRESS DURING LABOR. CURTIS J. LUND, Illinois M. J. **83**:96 (Feb.) 1943.

Anoxia is responsible for many fetal deaths and may produce temporary or permanent damage in the central nervous system. It is a factor in the production of neonatal asphyxia.

As prophylaxis, any complication of pregnancy or labor which may endanger the oxygen supply of the fetus should, if possible, be corrected. One should anticipate fetal and neonatal asphyxia and be prepared to treat it. The administration of oxygen to the mother during and immediately after labor may be of benefit.

BARBOUR, Peoria, Ill.

RESPIRATORY DISTURBANCES IN THE NEWLY-BORN INFANT. EDITH L. POTTER, Illinois M. J. **83**:100 (Feb.) 1943.

Interference with neonatal respiratory activity, either in its primary establishment or in subsequent maintenance, is due largely to abnormalities which result from

environmental conditions. These may have existed prior to birth, or they may occur during or after birth. Less frequently the disturbance may be due to lesions intrinsic in the fetus.

Anoxia having its inception while the fetus is still in the uterus may result from a decrease in the oxygen content of the maternal blood or in the total amount of maternal blood reaching the placenta, from interference with oxygen exchange between the maternal and the fetal blood within the placenta or from interruption of the circulation between the placenta and the fetus. During birth, anoxia may be produced by any of these conditions and, in addition, by trauma which causes intracranial hemorrhage and produces injury of the respiratory center. After birth the initial establishment of respiration may be inhibited, or breathing may subsequently become arrested, either from the late effects of previously induced anoxia or from conditions intrinsic in the fetus and functioning for the first time after birth. The latter include immaturity or maldevelopment of the respiratory center, immaturity or maldevelopment of the pulmonary alveoli, occlusion of the trachea, bronchi or alveoli by amniotic debris, blood from hemorrhage or leukocytic exudate, prevention of alveolar expansion by external pressure as in pneumothorax, diaphragmatic hernia, pleural or peritoneal effusions, excessive cardiac hypertrophy, and renal polycystitis. Abnormal breathing which makes its first appearance a few hours after birth may be associated with increase in cerebrospinal fluid within the subarachnoid space; it is most often found after cesarean section. The condition may be fatal, or recovery may occur. BARBOUR, Peoria, Ill.

CARBONIC ANHYDRASE IN NEWBORN INFANTS. STUART SHELTON STEVENSON, J. Clin. Investigation **22**:403 (May) 1943.

Because Meldrum and Roughton had found goat fetuses low in carbonic anhydrase, because carbonic anhydrase is found with hemoglobin in the red blood cells and because of a clinical impression that some premature and full term newborn infants who were doing poorly and who were exhibiting cyanosis improved after transfusions of whole blood, an attempt was made to correlate unexplained cyanosis in newborn infants with low concentrations of carbonic anhydrase in the blood.

The concentration of carbonic anhydrase in the blood of newborn infants is less than one half and the concentration in premature infants is only one quarter of that found in the blood of adults. Spontaneous changes in the blood enzyme level do not usually occur, but significant increase in the level can be accomplished by transfusions of whole blood.

Thirteen infants were studied who exhibited cyanosis, unexplained by recognized physical causes, and who were doing poorly. In many instances these infants showed levels of carbonic anhydrase which were significantly low. Improvement in respect to cyanosis and general condition was accompanied by a rise in the blood concentration of carbonic anhydrase. The rise occurred in one infant spontaneously and was minimal. In the remaining infants the rise followed transfusion and was significant in most instances.

The findings show that many premature infants who are doing poorly and exhibit cyanosis have low levels of carbonic anhydrase. Following transfusions of adult blood the level of carbonic anhydrase increases and clinical improvement, accompanied by a disappearance of cyanosis, follows. [AUTHOR'S SUMMARY.]

THE RH FACTOR IN RELATION TO JAUNDICE OF THE NEWBORN INFANT (ERYTHROBLASTOSIS FETALIS). FRED W. GALLAGHER, PETER G. DANIS and LLOYD R. JONES, J. Pediat. **22**:171 (Feb.) 1943.

For a group of 20 mothers who had severely icteric infants, determinations of the Rh factor were made; 11 of the 20 had Rh-negative blood and 9 Rh-positive blood. This did not agree with the results obtained by Levine, who reported a relationship of mother with Rh-negative blood and baby with Rh-positive blood in 90 per cent of cases of erythroblastosis. Furthermore, Rh antibodies, found in only 3 of the 11 mothers with Rh-negative blood, had no relationship in titer to the severity of the disease. The authors thus feel that in the diagnosis of erythroblastosis fetalis the laboratory determination of the Rh factor is of limited value.

STETTENBENZ, Buffalo.

DISTURBED KIDNEY FUNCTION IN THE NEWBORN INFANT ASSOCIATED WITH DECREASED CALCIUM: PHOSPHORUS RATIO. C. E. SNELLING, J. Pediat. **22**:559 (May) 1943.

During investigation of cases of tetany of the newborn it was observed that, in addition to disturbed calcium balance, several infants had retention of nitrogen and phosphorus. Apparently, in a large number of these cases the tetany was the result of renal retention, either permanent or temporary. Eleven cases are presented in detail. All of the patients had symptoms usually described in infantile tetany: twitching, carpopedal spasm, cyanosis or convulsions; most of them showed a lowered level of calcium, and all showed elevated levels of phosphorus and nonprotein nitrogen. In 2 patients renal abnormalities incompatible with life were observed at autopsy. Those who recovered under treatment with calcium gluconate and intravenous injections of dextrose in saline solution showed a fairly quick drop in the values of nonprotein nitrogen and phosphorus and a rise in calcium to normal levels with the disappearance of symptoms of tetany. STETTENBENZ, Buffalo.

THE CAUSES OF FETAL AND NEONATAL DEATH. AGNES R. MACGREGOR, Edinburgh M. J. **50**:332 (June) 1943.

Four principal causes of fetal and neonatal deaths are developmental malformation, intracranial hemorrhage, asphyxia and infection. The writer urges that every maternity hospital should have a pathologist who is interested and experienced in neonatal pathology. Accuracy in the clinical diagnosis of neonatal disorders sometimes is difficult, so that determination of the cause of death, when there is no autopsy, is impossible.

NEFF, Kansas City., Mo.

HAEMANGIOMA OF ARM CAUSING DELAY IN DELIVERY AND NEONATAL DEATH. MILDRED I. EALING, J. Obst. & Gynaec. Brit. Emp. **50**:144 (April) 1943.

A cystic hemangioma encircling the left arm and extending from ¼ inch (0.6 cm.) above the wrist to 1½ inches (3.8 cm.) below the acromion was of sufficient size to delay delivery. It also caused mechanical obstruction to the circulation which produced death from cardiac failure on the third day. POTTER, Chicago.

A CASE OF ACUTE SCLEREMA. R. T. KENNEDY, M. J. Australia **1**:463 (May 22) 1943.

The author reports a case of acute sclerema which appeared on the fourth day of life and in which gen-

eralized solidification of the subcutaneous fat developed so rapidly as to cause death in a few hours. The types of neonatal sclerema are briefly discussed.

GONCE, Madison, Wis.

THE RH FACTOR AND ITS APPLICATION TO OBSTETRIC PRACTICE. G. S. ADAM, M. J. Australia **1**:507 (June 5) 1943.

A lucid discussion of the current conception of the Rh factor is presented. Of particular interest is the statement that Brisbane Woman's Hospital has established a bank of known Rh-negative blood.

GONCE, Madison, Wis.

## Acute Contagious Diseases

THE RELATION OF THE CARRIER TO EPIDEMIC MENINGITIS. J. HOWARD MUELLER, Ann. Int. Med. **23**:974 (June) 1943.

In all probability a large proportion of our population is relatively immune to epidemic cerebrospinal meningitis. The nasopharynx, usually, is a barrier to the passage of meningococci. Prophylactic administration of the sulfonamide drugs may temporarily eradicate carriers, but the effects are not lasting. No other means are available for prophylaxis.

READING, Galveston, Texas.

OBSERVATIONS ON IMMUNITY IN MUMPS. JOHN F. ENDERS, Ann. Int. Med. **23**:1015 (June) 1943.

The serums of 265 adults and 115 children were tested for epidemic parotitis antibody. Antibody occurred in the serum of 92 per cent of those giving a history of mumps, and 50 per cent of those who denied having had the disease previously. It is reasonable to conclude that 50 per cent of those who said they had not had mumps must at some time have had a "silent" infection which would be sufficient to render them insusceptible.

READING, Galveston, Texas.

ATTEMPTS TO PROPAGATE THE VIRUS OF POLIOMYELITIS IN SMALLER LABORATORY ANIMALS. JOHN L. SCHWAB, ORAM C. WOOLPERT and N. PAUL HUDSON, J. Infect. Dis. **72**:97 (March-April) 1943.

Attempts were made to adapt the virus of poliomyelitis to fetal animals of several species (guinea pigs, rabbits, white mice, white rats) and to postnatal animals of these and other species (guinea pigs, rabbits, white mice, cotton rats, pigeons and chickens).

Eight strains of poliomyelitis virus were used, among which were the standard MV strain, strains adapted to the cotton rat and strains isolated from man by passage through monkeys.

Various methods of inoculation and manipulation were employed, including intracranial inoculations in utero, intraocular inoculations, cerebral injections of virus mixed with starch and with liquid petrolatum, subcutaneous injections and intranasal instillations of virus plus Toomey's "Bacillus coli toxic filtrate," and intracerebral inoculation after ligation of the carotid arteries. Tissues were examined for the presence of the virus after various incubation periods and after blind serial passages.

Although the virus persisted for a short time in the nerve tissue of fetal animals and it was occasionally transmitted through a few serial passages, neither this technic nor any of the other methods employed resulted in an adaptation of the virus to new experimental animals.

In monkeys and cotton rats whose carotid arteries had been ligated, susceptibility seemed increased, since the incubation periods were shortened and higher dilutions of the virus preparation were infective.

TOOMEY, Cleveland.

RELATION BETWEEN AMOUNTS OF PERTUSSIS ANTIGEN INJECTED AND PRODUCTION OF AGGLUTININS. JOHN A. TOOMEY, W. S. TAKACS, ROY AVERILL and NORMAL LEWIS, J. Lab. & Clin. Med. **28**:835 (April) 1943.

The authors describe experiments in which phase B Haemophilus pertussis organisms (phase IV of Leslie and Gardner) were given to rabbits. Following is the authors' summary:

"1. Rabbits given 10 doses of phase B H. pertussis organisms standardized in toxin at 20 mg. per cubic centimeter have a higher agglutinin titer against phase B organisms than do the blood serums of those given the same number of doses of 4 mg. per cubic centimeter. Both antigens produced only a negligible titer of agglutinins against phase A organisms, the type which initiates the disease in man.

"2. Four milligrams, 20 mg. and 45 mg. of phase B organisms for ten injections will produce nearly comparable agglutinin titers in rabbits against phase B organisms and some demonstrable but not marked agglutinins against heterologous phase A bacilli.

"3. When rabbits are injected weekly over a long period with massive amounts of phase B organisms as the antigen, there is no increase in titers against the phase B organisms, but in some instances there may be an increase in the agglutinin titer against phase A bacilli as high as 1:160."

WILKINSON, Galveston, Texas.

CLINICAL RESULTS WITH THE USE OF AGGLUTINOGEN FROM PHASE I HEMOPHILUS PERTUSSIS AS A SKIN TEST FOR SUSCEPTIBILITY TO WHOOPING COUGH. HARRIET M. FELTON and EARL W. FLOSDORF, J. Pediat. **22**:259 (March) 1943.

Using the purified agglutinogen of Haemophilus pertussis phase I, the authors made cutaneous tests on 776 children to determine the presence or absence of immunity to pertussis. The reactions are interpreted as follows:

1. Positive (immune). A well indurated reaction (with or without erythema) 20 mm. or more in diameter at either one-half hour or twenty-four hours or both.

2. Weekly positive (immune). A reaction not exceeding 20 mm. but at least 10 mm. in diameter at one-half hour or twenty-four hours or both.

3. Negative (susceptible). No indurated reaction at one-half hour to twenty-four hours.

Of great significance was the testing of 94 infants, aged 6 to 14 months, for whom no history of pertussis or immunization was obtained; all tests showed negative (susceptible) reactions. Of 305 children with histories of previous vaccination who were tested three months to five years after immunization, 112 showed weakly positive (immune) reactions and 170 positive (immune) reactions; 23 gave negative reactions. Unfortunately, 225 children had been given a pertussis vaccine of questionable potency. Of 26 given proper immunization none showed a negative reaction. The remaining children were those either with a history of pertussis

or with unknown history. Miscellaneous results were obtained, but most of the subjects with a definite history of pertussis gave an immune response. Serum titers were also checked, and there was found to be definite correlation between the intensity of the reaction and the height of the titer. Of great clinical importance is the rapid boost in the agglutination titer of the serum after cutaneous tests with agglutinogen in persons with an existing complete or partial immunity to pertussis. This was clearly shown in the study of an epidemic occurring in a small institution. The titer also persisted for months at a high level. It was also possible by repeated cutaneous inoculation to reverse a negative (susceptible) reaction to a positive (immune) reaction with a corresponding rise in serum titer. Thus the possibilities in immunization as well as in therapy through the use of this purified agglutinogen are indeed promising.

STETTENBENZ, Buffalo.

MIXED IMMUNIZATION IN INFANCY AND CHILDHOOD. JOSEPH H. LAPIN, J. Pediat. **22**:439 (April) 1943.

An evaluation of five methods of combined and simultaneous immunization against diphtheria, pertussis and tetanus was made by Lapin, based on the treatment of 50 children.

The children in the first group were given three injections of pertussis vaccine (total dose, 80,000,000,000 organisms) followed by three injections of clear diphtheria toxoid and, last of all, two injections of alum-precipitated tetanus toxoid.

The second group received three injections of alum-precipitated combined pertussis and diphtheria toxoid, followed by alum-precipitated tetanus toxoid.

The subjects in group 3 were given pertussis vaccine and simultaneously two injections of alum-precipitated combined tetanus and diphtheria toxoid.

A fourth group received combined alum-precipitated pertussis vaccine, diphtheria toxoid and tetanus toxoid.

The children in group 5 were given three monthly injections of pertussis vaccine, followed by two doses of combined alum-precipitated tetanus and diphtheria toxoid.

Results definitely showed that group 5 had the highest immunity titers for diphtheria, pertussis and tetanus, and that the method for this group produced the mildest local and systemic reactions. Group 1 had the poorest levels of diphtheria and tetanus antitoxin titers. The methods used for groups 2 and 4 evoked severe inflammatory and febrile responses in all, with formation of alum abscesses in 2 children. In group 3 fair immunity titers were achieved but there were more inflammatory and systemic reactions than in group 1.

The method used for the children in group 5 is the one recommended by the author.

STETTENBENZ, Buffalo.

WHOOPING COUGH VACCINES. JOSEPH H. LAPIN, J. Pediat. **22**:452 (April) 1943.

Whooping cough vaccine produces febrile and inflammatory reactions in many children. Lapin has searched for the component responsible, using variously prepared vaccines. He found that living suspensions and suspensions sensitized by the addition of immune serum and alum-precipitated vaccines had no immunologic advantages and produced more severe reactions than regular pertussis vaccines. Neither the blood used in the preparation of the vaccine, human, bovine or ovine, nor the preservatives used caused reactions.

Lapin feels that the weakly antigenic toxic component in Hemophilus pertussis vaccines is responsible, and he suggests a method for the preparation of vaccine which will almost completely remove this factor, leaving the more potent antigenic, agglutinogenic, nontoxic component present.

STETTENBENZ, Buffalo.

TONSILLECTOMY AND POLIOMYELITIS: A NEW CONCEPT OF ETIOLOGICAL RELATIONSHIP. W. J. MCCORMICK, M. Rec. **156**:164 (March) 1943.

The question is raised as to whether there is any relationship between the lymphatic hypertrophies which precede tonsillectomy and are frequently associated with poliomyelitis and nutritional deficiency (especially deficiency in vitamin B complex). The author also suggests that anoxia occurring during surgical anesthesia may be related to the incidence of poliomyelitis following that operation. McCormick also raises the question of the possible endogenous origin and biochemical nature of the virus.

FERDINAND, Peoria, Ill.

REPORTED WHOOPING COUGH MORBIDITY AND MORTALITY IN THE UNITED STATES. C. C. DAUER, Pub. Health Rep. **58**:661 (April 23) 1943.

Beginning in 1925, mortality from whooping cough began to decline so rapidly that the rate for 1935 to 1939 was only 1.8, a decline of 80 per cent in fifteen years. This is not due to a lessening of the disease, for from 1910 to 1939 the morbidity rates increased. There are higher than average death rates from whooping cough in the southern and mountain states and in the rural population. If the rate continues to decline as it has, it will be very difficult to demonstrate that prophylatic procedures have any effect in reducing the mortality from this disease.

SANDFORD, Chicago.

POLIOMYELITIS IN THE UNITED STATES IN 1942, AND A SUMMARY OF ITS PREVALENCE FROM 1933 TO 1942 INCLUSIVE. C. C. DAUER, Pub. Health Rep. **58**:937 (June 18) 1943.

This article is an excellent review of poliomyelitis in the United States; it includes the distribution by counties, the morbidity and mortality by states, the periodicity of outbreaks, the age distribution and the epidemiology. It cannot be abstracted but should be read in full by any one interested in the subject.

SANDFORD, Chicago.

SURGICAL SCARLET FEVER. MAX J. FOX and MAURICE HARDGROVE, Wisconsin M. J. **42**:402 (April) 1943.

"Surgical scarlet fever" is a syndrome resembling classic scarlet fever. It differs mainly in that the focus of bacterial invasion and of toxin production is elsewhere than in the throat. It frequently follows traumatic or surgical implantation of hemolytic streptococci into a wound.

Four cases are presented, in all of which the organism was found culturally to be the same and in which the toxin was neutralized by commercial scarlet fever antitoxin and by convalescent serum.

JANNEY, Wauwatosa, Wis.

POLIOMYELITIS: MODERN VIEWS OF ETIOLOGY AND EARLY DIAGNOSIS. W. G. MYLLIE, Practitioner **150**:219 (April) 1943.

This article is a comprehensive, general review of the present theories concerning the portals of entry of the virus of poliomyelitis and of the diagnosis and treatment of the disease.

THELANDER, San Francisco.

DISCUSSION ON THE PROPHYLAXIS OF THE ACUTE SPECIFIC FEVERS. E. H. HARRIES, A. W. DOWNIE and R. E. SMITH, Proc. Roy. Soc. Med. **36**:271 (April) 1943.

Dr. Harries, in a summary of his discussion on the prophylaxis of acute specific fevers, brought out the following facts: To insure prophylactic measures a satisfactory environment and adequate nutrition must be provided, and parents and teachers must be educated in the importance of hygiene and of early medical advice for the correction of hypovitaminosis, anemia and dental sepsis. The poorer the environment, the greater the incidence of measles among children of preschool age, and the higher the proportion of cases complicated by bronchopneumonia. The school provides the locus from which the infection is carried to the child's home. The practitioner should be allowed to hospitalize a patient for confirmation of a suspicion when he sees him too late or too early for diagnosis. Isolation in a hospital removes an abundant reservoir of infection and so limits the number of contacts. The modern fever hospital should have first class laboratory assistance. The prophylaxis of measles, chickenpox and mumps gives disappointing results. With the aid of the Schick and Dick tests a school community can be divided into safe and unsafe groups; the latter either are susceptible and in danger themselves or are immune carriers and therefore dangerous to others.

Dr. Downie stated that the incidence of pertussis is highest in the age group 3 to 7 years but that the highest mortality is in the first year of life. He then discussed the prevention of whooping cough by vaccination, as practiced in the United States.

Dr. R. E. Smith outlined the prophylactic measures taken against the acute specific fevers in a residential school (Rugby). The report was accompanied by four tables and a chart. Table 1 and the chart showed the usual risks of infection the average public school boy was likely to run from birth up to the school-leaving age of 18 years. Table 2 listed the diseases with which the boys were in contact and the quarantine time advised. Table 3 showed the results of testing nearly six hundred boys for immunity against diphtheria, and table 4 the results of retesting after various intervals.

WILLIAMSON, New Orleans.

THE SCHICK REACTIONS AND DIPHTHERIA IMMUNISATION OF A SOUTH AFRICAN FIELD HOSPITAL STAFF IN THE MIDDLE EAST. B. M. BLOOMBERG, South African M. J. **17**:99 (April 10) 1943.

Among 241 adult subjects who had neither been immunized to diphtheria nor had the disease, 38 per cent had positive Schick reactions. There was a high difference in the proportion of positive reactions in men and in women: 60 per cent of the nursing sisters and probationers, as compared with 25 per cent of the medical officers and male personnel of other ranks, had positive reactions. There was no significant difference between the nursing sisters and the probationer nurses, although the latter had been engaged in nursing only since the commencement of war. This has been taken to indicate that the degree of exposure of members of the nursing profession in South Africa to diphtheria has not been great. An analysis of the data in relation to age suggests that once adult life is reached there are no significant variations with age in the percentage of persons with positive Schick reactions. Positive Moloney reactions were more frequent and more severe in subjects who had negative Schick reactions. It is therefore preferable to postpone the Moloney test until the Schick reaction has been determined. No apparent advantage could be discerned in commencing immunization with smaller doses of toxoid in persons who reacted severely to the Schick and Moloney tests; it is advisable to avoid immunization with formaldehyde-treated toxoid altogether in such adults.

GONCE, Madison, Wis.

LARYNGOTRACHEOBRONCHIAL DIPHTHERIA. J. M. TATO and E. O. BERGAGLIO, Rev. Asoc. méd. argent. **57**: 155 (April 15-30) 1943.

Diphtheria is a disease which in its malignant and invasive form has a high mortality. The authors studied the laryngotracheal and tracheobronchial diphtherias because they produce the highest mortality and are most easily confused with other bronchopulmonary infections. Brief reviews are presented of the symptoms which are useful in the differentiation of the obstructive, toxic and cyanotic forms and of the etiologic diphtheritic factors. The authors diagnose tracheobronchial diphtheria by (1) clinical observations, (2) endoscopic examination, (3) bacteriologic studies, (4) therapeutic tests and (5) roentgenologic means. With the aid of the endoscope they not only inform themselves of the state of the larynx but frequently remove all or portions of the pseudomembrane. Serum therapy is kept at a high level. The roentgen study assists by locating areas of atelectasis for further observation with the endoscope. The authors conclude that endoscopic examination is essential for accurate diagnosis of laryngotracheal and/or tracheobronchial diphtheria. Early diagnosis is necessary to successful treatment; the latter includes removal of the membranes and intensive administration of serum.

ZETTELMAN, Evanston, Ill.

NONPARALYTIC FORMS OF HEINE-MEDIN DISEASE [ACUTE ANTERIOR POLIOMYELITIS]. ENRIQUE A. BERETERVIDE, Rev. de hig. y med. esc. **2**:7, 1943.

Until eight or ten years ago, the characteristics of such forms of acute anterior poliomyelitis (Heine-Medin disease) as are unaccompanied by paralysis were known in Argentina only through investigations made in the United States of America (Park, Paul, Toomey), Denmark (Jensen, Nissen and others) and Australia (McDonald, Zebott).

It was just recently, since the epidemics in 1936, 1939-1940 and 1942-1943, that physicians in Argentina learned to recognize these forms of the disease. As can be easily understood, the existence of atypical forms has an incalculable prophylactic significance.

The nonparalytic forms of poliomyelitis may be subdivided into the abortive meningeal and latent forms.

The abortive form is that in which there appears to be no direct involvement of the nervous system. The diagnosis up to now, and until a conclusive laboratory method for identification is developed, is made only during epidemics. At those times poliomyelitis must be suspected in certain serious infectious illnesses with high temperature, profuse sweating and great depression which disappear in forty-eight hours to four days without leaving traces other than a pronounced asthenia.

The pure meningeal form is characterized by changes in the spinal fluid, extreme rigidity of the neck and the vertebral column, headache and vomiting. These clinical signs persist for two weeks after the fever has subsided.

The latent form is characterized by transitory neuromuscular symptoms, slight paresis and hyporeflexia, which may pass unnoticed unless a careful examination

is made. Patients with this form of poliomyelitis recover, with only slight, transitory paralytic sequels showing that the nervous system has not been uninjured. Examination of the spinal fluid in this form of the illness, as in the abortive form, does not supply any valuable data. [FROM THE AUTHOR'S SUMMARY.]

## Acute Infectious Diseases

ACUTE RHEUMATIC FEVER AND VALVULAR DAMAGE. M. G. BROWN, Am. Heart J. **25**:686 (May) 1943.

The author arrives at the following conclusions:

"1. There is no relationship between the character of rheumatic fever, the number of recurrences and the age of the patient at onset on the one hand, and the development of cardiac damage on the other hand.

"2. If valvular damage develops in patients it usually does so after the first attack of rheumatic fever.

"3. The patient's immunity or resistance is the important factor in determining whether or not permanent valvular damage will occur."

GIBSON, Chicago. [AUTHOR'S SUMMARY]

DIPHYLLOBOTHRIUM LATUM IN FLORIDA. WILLIAM A. SUMMERS and PAUL P. WEINSTEIN, Am. J. Trop. Med. **23**:363 (May) 1943.

The authors report 3 cases of Diphyllobothrium latum infection occurring in Negro children in subtropical Florida. These infections in human beings were thought to be most probably of local origin.

BURPEE, Augusta, Ga.

ROLE OF TOXIN AND USE OF ANTITOXIN IN SYSTEMIC STAPHYLOCOCCIC INFECTIONS. BARNARD KLEIGER and JOHN E. BLAIR, Arch. Surg. **46**:548 (April) 1943.

Basing their conclusions on clinical and experimental studies, the authors state that some strains of staphylococci produce a potent exotoxin which is capable of exerting several well defined effects on different tissue cells. The outstanding results of the action of staphylococcus exotoxin are: hemolysis of red blood cells, destruction of leukocytes, necrosis of skin and subcutaneous tissues and necrosis of certain other tissues. A potent specific antitoxin was utilized in certain patients exhibiting the characteristic features of staphylococcic toxemia. The administration and dosage of the antitoxin are fully described. The patients, mostly children, exhibiting the characteristics of a true toxemia responded rapidly and well to the administration of staphylococcus antitoxin, while patients above 30 years of age and others who did not show evidence of toxemia did not respond to antitoxin in this manner.

KAISER, Rochester, N. Y.

RHEUMATIC FEVER IN CHILDREN. BETTY HUSE, Child **7**:158 (May) 1943.

The author emphasizes the fact that rheumatic fever is an acute disease requiring scrupulous care during its active phase, whether it is the first or a subsequent attack. Early recognition is of great importance. Death occurs almost always from the acute infection rather than from scarring of the heart; thus anything that can be learned about the prevention of recurrences is of utmost value. The results from the use of small daily doses of sulfanilamide are promising. The improvement of housing and of other social conditions which predispose the child to attacks are matters of public concern.

Much has been gained through the state programs, under the Social Security Act, for the care of these children. There is, however, great need for additional funds so that this work may be extended.

LESLIE, Evanston, Ill.

THE KAHN VERIFICATION TEST IN MALARIA. ALBERT DE GROAT, J. Lab. & Clin. Med. **28**:882 (April) 1943.

Studies on a group of clinically nonsyphilitic soldiers with malaria indicate that the Kahn test can be employed as an aid in establishing the differential diagnosis of malaria and syphilis.

WILKINSON, Galveston, Texas.

THE COMPARATIVE EFFECTIVENESS OF ARSENICAL COMPOUNDS AND SULFONAMIDE DRUGS AGAINST BACTERIAL INFECTIONS. EDWIN E. OSGOOD, J. Lab. & Clin. Med. **28**:953 (May) 1943.

Analysis of experiments on different bacteria by the marrow culture technic, comparing the effectiveness of arsenical compounds and the four most commonly used sulfonamide drugs, is presented. The author concludes that neoarsphenamine administered according to directions previously published by him deserves further trial in cases of subacute bacterial endocarditis and bacteremia, of endocarditis and of other serious infections due to Staphylococcus aureus, hemolytic streptococci, Haemophilus influenzae and Neisseria gonorrhoeae, and possibly as a local application in cases of diphtheria. Of the sulfonamide drugs, sulfathiazole would appear to be the one of choice.

WILKINSON, Galveston, Texas.

SUSCEPTIBILITY OF SHIGELLA PARADYSENTERIAE TO SODIUM SULFATHIAZOLE AND SULFAGUANIDINE IN VITRO, WITH SOME INFORMATION REGARDING EBERTHELLA TYPHOSA, SALMONELLA PARATYPHOSA, ESCHERICHIA COLI, SALMONELLA MORGANI AND PROTEUS. MERLIN L. COOPER and HELEN M. KELLER, J. Pediat. **22**:418 (April) 1943.

Cooper and Keller have studied the bacteriostatic and bactericidal effects of sodium sulfathiazole and sulfaguanidine in vitro on twelve strains of Shigella paradysenteriae Sonne and on fifteen strains of miscellaneous intestinal bacteria, all pathogenic. Cultures were thoroughly studied over a period of twenty-one days, and each strain was tested with nineteen different concentrations of the drug. Results clearly demonstrated that sulfathiazole was more bactericidal for the strains tested than was sulfaguanidine. Sulfathiazole was more effective for Flexner strains than for Sonne strains and less effective for Eberthella typhosa and Salmonella paratyphosa than for S. paradysenteriae.

STETTENBENZ, Buffalo.

A STUDY OF HUMORAL ANTIBODIES FOR STAPHYLOCOCCUS AUREUS IN INFANTS AND THEIR MOTHERS. J. A. LICHTY JR., CHRIS P. KATSAMPES and W. S. BAUM, J. Pediat. **22**:549 (May) 1943.

The authors determined the amounts of antitoxin and anticapsular agglutinins for Staphylococcus aureus in the blood of mothers and newborn infants. The two antibodies were present in each baby's blood in practically the same concentration as in the mother's blood, although the correlation was closer for antitoxin than for anticapsular agglutinins. The antitoxin level declined sharply during the first few months of life; how-

ever, the agglutinins remained fairly constant throughout the first year. In 30 cases, the infant had a higher content of antitoxin than the mother, in 18 they were identical and in only 2 was the infant's titer lower. The titer for agglutinins was identical with the mother's in 30 babies, lower in 16, and higher in 4.

Further study is necessary to interpret the role these antibodies play in protecting newborn infants from staphylococcic infections. STETTENBENZ, Buffalo.

VIEWS ON THE ORIGIN OF MALARIA IN 1843. Editorial, Edinburgh M. J. **50**:315 (May) 1943.

The *Edinburgh Medical Journal* in the last few years has reviewed various interesting subjects discussed in issues of one hundred years ago. This issue reports on an article by Henry McCormack, M.D., of Belfast, "Opinions on the Origin of Malaria," from volume 60, 1843. McCormack stated the belief that malaria was a result of vegetable decomposition in combination with a warm climate, and that if the temperature of the air remained steadily below a certain level malaria was never generated even in marsh or lush lands. He added: "It is not, perhaps, likely that these remarks will convince those from whom I have the misfortune to differ; but they will, perhaps, help to set the question of the real and only origin of malaria in a clearer light, and thereby assist those who are anxious to arrive at a correct decision in forming their conclusions."

NEFF, Kansas City, Mo.

SUBCUTANEOUS NODULES IN RHEUMATISM. J. C. BANERJEA, Indian J. Pediat. **10**:41 (April) 1943.

During the past eight years Banerjea encountered 717 cases of cardiac disease in his hospital and private practice in Calcutta, India, in 320 of which the condition had a rheumatic origin. Among these, 181 were cases of juvenile rheumatism (0 to 20 years), in 15 of which there were rheumatic nodules, an incidence of 8.2 per cent. Of the 15 patients with rheumatic nodules, 8 (53.3 per cent) were in the age group 11 to 15 years, 5 (33.3 per cent) in the group 6 to 10 years and only 2 (13.3 per cent) in the group 16 to 20 years. Rheumatic nodules were not seen in any child under 8 years. Girls constituted only 20 per cent of the total number of patients with nodules. The nodules in most cases occurred around the elbows. The next most frequent sites were the tendons of the feet, ankles and knees, and the tendons of the fingers, forearms and wrists. The average number of nodules was six; the maximum number was twenty-eight. Death occurred from congestive failure within three weeks of the appearance of the nodules in a boy of 10 years and within a month in a girl of 13 years. The other patients with nodules, unfortunately, could not be followed up.

GONCE, Madison, Wis.

BACILLARY DYSENTERY CAUSED BY BACTERIUM DYSENTERIAE P274. L. ROTHSTADT, F. FENNER and B. BAKER, M. J. Australia **1**:341 (April 17) 1943.

In 42 of 85 cases of bacillary dysentery occurring endemically in a camp area in North Central Queensland, the infection was found to be due to Bacterium dysenteriae P274. Evidence is presented in support of the acceptance of this organism as a true dysentery bacillus. The authors suggest that the organism be named "B. dysenteriae Boyd IV."

GONCE, Madison, Wis.

BACILLARY DYSENTERY: SOME RESULTS AND CONCLUSIONS FROM A SERIES OF PATIENTS TREATED WITH SULPHAGUANIDINE. R. F. WEST, M. J. Australia **1**:344 (April 17) 1943.

The results in 23 patients with bacillary dysentery treated with sodium sulfate and in 74 treated with sulfaguanidine are compared. Patients treated with sulfaguanidine showed a pronounced improvement in their condition after twenty-four hours, and on the third day their feeling of well-being was remarkable; those receiving saline therapy experienced abdominal discomfort, anorexia and malaise for seven days and sometimes well into the second week. The stools first became normal with saline therapy on the fifteenth day and with sulfaguanidine therapy on the seventh. Sigmoidoscopic appearances became normal under saline therapy on the twentieth day and under sulfaguanidine therapy on the twelfth day. Complications due to the sulfaguanidine were as follows: severe constipation (15 per cent), headache and dizziness (4 per cent), morbilliform rash (4 per cent) and conjunctivitis (2 per cent).

GONCE, Madison, Wis.

EXPERIMENTAL IMMUNIZATION OF VOLUNTEERS AGAINST INFLUENZA VIRUS B. D. R. BULL and F. M. BURNET, M. J. Australia **1**:389 (May 1) 1943.

Of 23 subjects chosen for low titer of the antibody for influenza virus B, 21 showed a significant rise in antibody level after the primary administration of virus by the intranasal route, while only 2 showed any rise after the second administration, three to six months later. These results indicate that the procedure is likely to provide a substantial protection against natural influenza B. On the other hand, the proportion of minor symptoms was greater after the second inoculation than after the first. GONCE, Madison, Wis.

INTRANASAL VACCINATION OF HUMANS WITH LIVING ATTENUATED INFLUENZA VIRUS STRAINS. J. MAWSON and C. SWAN, M. J. Australia **1**:394 (May 1) 1943.

Although the average increase in antibody against each of the three strains in the vaccine (two strains of A and one of B) in 100 subjects was approximately twofold, the individual responses varied from no increase to a twenty-seven fold increase. In the majority of the persons who showed no increase in antibody after the first vaccination, repetition failed to raise the level. It is quite probable that these subjects almost all fall in the 50 to 90 per cent who do not contract influenza, even in pandemic periods; conversely, the people responding to the nasal vaccine are probably those who are susceptible to an infection of the respiratory tract such as influenza.

GONCE, Madison, Wis.

THE DIAGNOSIS OF ACUTE RHEUMATISM IN CHILDHOOD. C. BRUCE PERRY, Practitioner **150**:213 (April) 1943.

Under the diagnosis of this condition the author discusses involvement of joints, the salicylate test, growing pains and pains from other causes, fever, antecedent infections, cardiac involvement, subcutaneous nodules and erythema. Also he outlines the differential diagnosis of some other conditions sometimes confused with acute rheumatism, such as scurvy, poliomyelitis, osteomyelitis, acute leukemia and acute appendicitis.

THELANDER, San Francisco.

## Chronic Infectious Diseases

CARDIOVASCULAR INVOLVEMENT IN CONGENITAL SYPHILIS. J. HINRICHSEN, Am. J. Syph., Gonor. & Ven. Dis. **27**:319 (May) 1943.

From an exhaustive review of the literature it is concluded that congenital syphilis produces myocardial lesions of two types, namely, interstitial and nodular myocarditis, in which spirochetes can be demonstrated. No evidence could be found that congenital syphilis produces valvular cardiac lesions. The role of this disease in the production of aortitis and aneurysm and in the production of congenital malformation of the heart has not been determined definitely. Syphilitic arteritis, particularly cerebral arteritis, may be produced by congenital syphilis. It is possible that congenital syphilis is a factor in the production of arteriosclerosis and of Raynaud's disease. Congenital syphilis is one of the causes of hemorrhagic disease of the newborn.

REUTER, Milwaukee.
[ARCH. DERMAT. & SYPH.]

PULMONARY CALCIFICATION AND TUBERCULIN SENSITIVITY AMONG CHILDREN IN WILLIAMSON COUNTY, TENNESSEE. R. S. GASS, E. F. HARRISON, RUTH R. PUFFER, H. C. STEWART and W. C. WILLIAMS, Am. Rev. Tuberc. **47**:379 (April) 1943.

Continuation of an investigation which had its beginning several years ago confirms the authors' observations of a high frequency of calcified lesions in the pulmonary fields and the tracheobronchial lymph nodes of the children living in this region. This later study revealed the presence of such calcification in 83 per cent of the white and 72 per cent of the Negro school children. Two remarkable previous observations were also confirmed: that the prevalence of these lesions in the group of children 7 to 9 years of age was approximately as high as the prevalence in older children and that calcification occurred almost as frequently among children with negative reactions to tuberculin as among children with positive reactions. In the interval between survey calcification developed in a number of children, all of them under 15 years of age.

SMITH, Ogden, Utah.

GASTRIC LAVAGE AND SPUTUM CULTURES. JOSEPH L. ROBINSON and WILLIAM T. DUNN, Am. Rev. Tuberc. **47**:413 (April) 1943.

According to the technic advised for the collection of gastric contents, the patient refrains from taking food or drink overnight, and lavage of the fasting stomach is done in the early morning. A Levin tube is passed through the nostril, and aspiration is performed. Then 1 ounce of water is injected through the tube and immediately withdrawn. The treated and centrifuged sediment is stained and examined, and cultures are made on each of two mediums, Seenz' modification of Petrognani's medium and Jensen's modification of Löwenstein's. In a considerable series of cases both culture and animal inoculation of the sediment was done. The guinea pig test gave positive results in 24.4 per cent and the culture in 22.5 per cent of the cases. However, variations in the amount of material used for culture and for inoculation showed that considerable differences in results might be obtained and that the larger the amount of material used the greater the likelihood of positive results, either on animal inoculation or on culture.

SMITH, Ogden, Utah.

EFFECTS OF SMALLPOX VACCINATION (VACCINIA) ON SEROLOGIC TESTS FOR SYPHILIS. GRANT O. FAVORITE, Proc. Soc. Exper. Biol. & Med. **52**:297 (April) 1943.

Of 202 recently vaccinated persons (mostly nurses and medical students), 19 were found to have plus-minus to 4 plus reactions to one or more of the following tests: Kahn, Kolmer and Mazzini. Also one month after vaccination 4 of 25 persons who previously had negative serologic reactions were found to have positive reactions. Most of the reactions were 2 plus or less in intensity. These false reactions may persist for two months or more, but they disappear by the end of one hundred and twenty days. HANSEN, Minneapolis.

MODERN TRENDS IN PREVENTIVE AND SOCIAL ASPECTS OF TUBERCULOSIS. CHRISTOPHER CLAYSON, Edinburgh M. J. **50**:208 (April) 1943.

Sixty years ago tuberculosis was responsible for 16 per cent of the deaths in Scotland, but it now causes only 5.5 per cent and has dropped from the first to the fifth place among fatal diseases.

The writer outlines the functions of various units of what he terms "the tuberculosis scheme." Among these are: the dispensary, in which persons suspected of having tuberculosis and contacts are examined; the sanatorium, for the treatment of certain patients, and the hospital, for patients with more serious conditions. Persons discharged from the hospital or sanatorium frequently need rehabilitation in special colonies. Young children and old people are unsuited to this industrial rehabilitation. Statistics from mass roentgen examinations will reveal the type of distribution resulting from occupational contacts as contrasted with familial contaminations.

Reduction of the incidence of infection in dairy cows must be a part of the scheme for the control of tuberculosis. Probably one half of the cattle were infected before the war. At present, about 8 to 10 per cent of milk samplers are found to have tubercle bacilli, and about 3,000 persons are infected with bovine tuberculosis. A method of building up tuberculosis-free herds began in 1937, consisting of voluntary and if necessary compulsory testing, with destruction of infected animals. Financial encouragement has been practiced, as yet on a small scale, by giving a bonus to producers of milk from healthy herds. NEFF, Kansas City, Mo.

PROGNOSTIC BLOOD TESTS IN TUBERCULOSIS. JOHN T. PATERSON, Edinburgh M. J. **50**:288 (May) 1943.

A comparison of the reliability of four prognostic blood tests for tuberculosis is made, based on clinical and roentgenologic observations. The study comes from Southfield Sanatorium Colony, Edinburgh. In the series of cases observed the erythrocyte sedimentation rate was 80 per cent accurate as a basis for prognosis, while the total white cell count, the Weltmann serum reaction and the Medlar leukocyte index were less accurate, in the order named. NEFF, Kansas City, Mo.

A REPORT ON THE FLOCCULATION TEST OF MAZZINI. ANTONIO SELLEK and ALEJANDRO DEL FRADE, Arch. de med. inf. **13**:105 (April-June) 1943.

The authors compared the Mazzini flocculation test for syphilis with the Kahn and Sellek-Frade tests in 510 clinical cases. They report that the Mazzini test is more delicate than the others. SANFORD, Chicago.

## Diseases of Blood, Heart and Blood Vessels and Spleen

THE RELATIONSHIP OF CONGENITAL HEART DISEASE TO PREMATURE BIRTH. E. ARAYA and P. D. WHITE, Am. Heart J. **25**:449 (April) 1943.

The authors summarize the results of their study as follows:

"1. At autopsy, of 139 prematurely born children we found only 3 (2.2 per cent) with congenital malformation of the heart.

"2. Among 148 patients with congenital heart disease whose birth weight was known, we found 17 who weighed less than 2,500 Gm. at birth, that is, 11.4 per cent. In 172 cases in which the duration of pregnancy was ascertained, there were 17 patients who were born prematurely, that is, 9.8 per cent.

"3. In our cases the incidence of prematurity of birth among infants with congenital heart disease was about twice that among infants with normal hearts. Nevertheless, it happened that only 1 of 19 patients with patency of the ductus arteriosus (in reality a postnatal development) of this series weighed less than 2,500 Gm. at birth; all 4 patients with auricular septal defects were born at full term, and only 2 of 13 patients with the tetralogy of Fallot were born prematurely."

GIBSON, Chicago. [AUTHORS' SUMMARY]

ENDOCARDIAL FIBROELASTOSIS (SO-CALLED FETAL ENDOCARDITIS): A REPORT OF TWO CASES OCCURRING IN SIBLINGS. TOBIAS WEINBERG and ALBERT J. HIMELFARB, Bull. Johns Hopkins Hosp. **72**:299 (May) 1943.

The cases of 2 siblings with fibroelastosis of the endocardium are reported. This coincidence would imply that endocardial fibrosis is a developmental defect rather than an endocarditis due to intrauterine infection.

LYTTLE, New York.

BLOOD AMYLASE ACTIVITY IN DISEASE OF CARBOHYDRATE METABOLISM AND IN NONDIABETIC PANCREATIC DISEASE. S. Z. SORKIN, J. Clin. Investigation **22**:329 (May) 1943.

The amylolytic activity of the blood of 25 normal patients was found to be between 0.5 and 5.5 mg. (average 2.6 mg.) of maltose per cubic centimeter of serum per hour, measured by the method described.

Normal values for blood amylase were obtained in 56 patients with diabetes, 11 patients with hepatocellular disease, 8 with other types of hepatic disturbance and 1 with glycogenosis. The increased amylolytic activity of the blood encountered in the 4 patients with disease involving the excretory function of the pancreas is in accord with the clinical and experimental observations of numerous other authors.

The normal value for blood amylase in patients with disturbances of disease of carbohydrate metabolism is offered as clinical evidence of the nonparticipation of amylase in intermediary carbohydrate metabolism.

[FROM THE AUTHOR'S SUMMARY.]

CIRCULATION TIME: A REVIEW OF PREVIOUS METHODS AND THE INTRODUCTION OF AMINOPHYLLIN [THEOPHYLLINE ETHYLENEDIAMINE] AS A NEW AGENT. HARRY KOSTER and STANLEY J. SARNOFF, J. Lab. & Clin. Med. **28**:812 (April) 1943.

The authors report the use of theophylline ethylenediamine to measure circulation time. The end point is a marked increase in depth of inspiration, which in many cases amounts to a gasp. It is an objective method with a sharp end point. The circulation time determined by this method averaged twelve and four-tenths seconds for 92 patients.

WILKINSON, Galveston, Texas.

EFFECT OF TOURNIQUETS ON VENOUS BLOOD SUGAR VALUES. WINIFRED C. LOUGHLIN, HERMAN O. MOSENTHAL and RUTH HALPERN, J. Lab. & Clin. Med. **28**:1165 (June) 1943.

The application of a venous tourniquet results in significant changes in the venous blood sugar, amounting to 20 or 25 mg. per hundred cubic centimeters increase or diminution from the control value. These studies indicate that for greatest accuracy a tourniquet should not be used in obtaining venous blood for the determination of sugar content.

WILKINSON, Galveston, Texas.

OBSERVATIONS ON HEMOLYSINS IN ACUTE HEMOLYTIC ANEMIA. HENRY G. PONCHER, HOMER F. WEIR and ISRAEL DAVIDSOHN, J. Pediat. **22**:387 (April) 1943.

An interesting case of acute acquired hemolytic anemia in a 4½ year old white girl is described in detail. This child had a history of allergic reactions since infancy—severe eczema and in addition urticarial and angioneurotic episodes after ingestion of certain foods, such as eggs, wheat, orange juice and oatmeal. Other than these allergic responses and two attacks of furunculosis with lymph node abscesses, the history records nothing of significance until the age of 4½ years, when pallor, anorexia, malaise, nausea and vomiting developed. On admission to the hospital she was a jaundiced, acutely ill child. The main physical changes, in addition to the jaundice, were enlargement of the spleen and liver and enlargement of the heart with a systolic bruit. Significant laboratory data were: hemoglobin, 3.3 Gm. per hundred centimeters; red blood cells, 970,000; platelets, normal; erythrocyte fragility, normal; reticulocytes, 90 per cent. The urine contained urobilinogen. The child was given a number of transfusions, and on three occasions reactions occurred; one was of an urticarial type, and the others consisted of severe chills, fever and hemoglobinuria. The cause of these reactions is of interest and will be described. In spite of repeated transfusions the level of hemoglobin could not be raised appreciably or even maintained, and a splenectomy was performed in the hope of arresting the hemolytic process. However, the picture remained the same. About two weeks after the operation the child died. The conditions observed at autopsy are described in the article.

The authors attempted, unsuccessfully, to determine the hemolysin responsible in this case. In spite of the presence of pronounced food allergy, all attempts to correlate the dietetic allergens with the hemolytic process were unsuccessful. After two transfusions had produced reactions, it was found that the patient's blood was Rh negative and that she had been consistently given transfusions of Rh-positive blood; hence agglutinins against Rh-positive blood had been built up in her serum. Further transfusions, of Rh-negative blood, were successful, until a transfusion with a new donor's blood, given at room temperature, produced a severe reaction, with hemoglobinuria. It was then discovered that the patient had cold agglutinins in her blood which caused clumping of cells readily at ice box and even at room temperatures.

The occurrence of these reactions suggests the great care that is necessary in giving transfusions to patients with hemolytic anemia, particularly when a number of transfusions must be given. Extremely sensitive cross matching needs to be carried out, and, as in this case, determination of the Rh factor is important.

STETTENBENZ, Buffalo.

HUMAN SERUM AND PLASMA IN DISEASES OF CHILDREN. ERLING S. PLATOU, New Orleans M. & S. J. **95**:547 (June) 1943.

Human serum and plasma have achieved a secure place as therapeutic agents for diseases of children. Both agents are superior to blood in acute and chronic infections, hypoproteinemia, severe disturbances of fluid equilibrium and in conditions exhibiting increased capillary permeability, such as burns, trauma and hemorrhage.

Convalescent or hyperimmune serum is effective in the prophylaxis and treatment of scarlet fever, measles, pertussis and mumps. Pooled convalescent serum is now recognized as the most effective agent against measles. The administration of pertussis hyperimmune serum to exposed or afflicted infants produces dramatic results. Convalescent and pooled normal adult serums for mumps seem to have prophylactic value if used promptly after exposure.

Transfusions of serum in cases of bacteremia produce an increase in complement to a point which is higher than can be accounted for by the complement contained in the transfused serum.

Plasma and serum can materially help in combating chronic infections in children in two ways: (1) by nonspecific effects on metabolism, (2) by conferring antibodies contained in plasma pools.

Disturbances in fluid equilibrium are often of greater importance than the underlying disease. In alkalosis, the therapeutic needs are saline solution, calcium gluconate or chloride and plasma. In acidosis, dextrose buffered with sodium lactate or bicarbonate, followed by plasma, is indicated. The restoration of protein values to reduce localized or generalized collections of intracellular fluid, by using plasma, has been attempted in nephrosis, with some success except in cases in which there has been a nephritic component.

Clinical judgment must determine the need for specific and group antibodies, for fluids, for electrolytes and for protein sufficient to maintain adequate circulating blood volume. Valuable guides are the protein content of the plasma, the number of red cells, the hemoglobin content, the hematocrit reading and the specific gravity of the blood.

The dosage of plasma must depend on the child's weight and the condition for which it is used. For specific antibodies doses vary from 10 to 100 cc. In chronic infections and in hypoproteinemia the dose should be gaged by physiologic levels.

A table illustrating the computation of the amounts of protein needed and a comprehensive bibliography are appended.

BERKLEY, Beverley Hills, Calif.

RAPID METHOD FOR OBTAINING ANTI-RH SERUM FROM GUINEA PIGS. BARBARA C. MCIVOR and S. P. LUCIA, Proc. Soc. Exper. Biol. & Med. **52**:293 (April) 1943.

Adult guinea pigs were given five intraperitoneal injections of rhesus monkey erythrocytes in increasing doses at forty-eight hour intervals. The initial inoculum was equivalent to 1 cc. of whole blood and the last to 3 cc. The animals were bled intracardially on the second day, and 5 of the 9 animals used were found to produce reliable diagnostic serums. There were no deaths. This method proved to be more rapid and less expensive than the previously developed method of obtaining anti-Rh serum for diagnostic use.

HANSEN, Minneapolis.

HYPOPROTHROMBINEMIA AFTER SALICYLATE ADMINISTRATION IN MAN AND RABBITS. S. RAPOPORT, MARY WING and GEORGE MARTIN GUEST, Proc. Soc. Exper. Biol. & Med. **53**:40 (May) 1943.

The administration of methylsalicylate produced no change in the prothrombin time in dogs, whereas it produced severe degrees of hypoprothrombinemia in rabbits. Of 15 rheumatic subjects 6 to 14 years of age who were receiving salicylates, 8 showed significant prolongation of the prothrombin time. The evaluation of the clinical significance of these changes has not been made.

HANSEN, Minneapolis.

STUDIES IN REFRACTORY ANEMIA. L. S. P. DAVIDSON, L. J. DAVIS and JAMES INNES, Edinburgh M. J. **50**:226 (April) 1943.

The authors recommend the use of the term "refractory anemia" as a convenient generic designation for the diverse forms of anemia resistant to treatment with hematinic agents. They believe such conditions are rare. The article deals with the technic and interpretation of sternal biopsies and proposes a classification, of three general types, for the resistant anemias.

NEFF, Kansas City, Mo.

FORMATION OF RED BLOOD CORPUSCLES. FREDERIC DURAN-JORDA, Lancet **1**:513 (April 24) 1943.

For several years the author had a strong conviction that the erythrocytes were a product not of cellular evolution but of cellular secretion. The study of slides of a 2.5 mm. human embryo and of sternal marrow proved to him that his conviction was correct. As a result of his investigations he arrived at the following conclusions:

"1. The red blood corpuscle is formed from the plasma cell. As the plasma cell occurs all over the body one must assume that the red blood corpuscle can be formed all over the body and not only in the blood marrow as is currently supposed.

"2. The red blood corpuscle is a secretion of the plasma cell and is formed when the plasma cell disintegrates.

"3. When the plasma cell disintegrates the nucleus is extruded with a small halo of protoplasm and this exists as an independent cell, corresponding to what is currently known as the normoblast.

"4. The red blood corpuscle is a simple droplet of colloidal nature and is in some respects similar to the fat globules in milk.

"5. The accepted lymphocyte is really a stage in the development of the normoblast.

"6. The platelets are really protoplasmic remnants of the original plasma cell which has broken up."

LANGMANN, New York.

## Diseases of Nose, Throat and Ear

SORE THROAT OUTBREAK IN AN UPSTATE HOSPITAL. Health News **20**:107 (June 28) 1943.

The milk-borne outbreak of 23 cases of sore throat that is reported is unique in that all the milk served in

the institution was pasteurized. Hemolytic streptococci were traced to a handler of milk in the hospital. Improper washing of milk containers was blamed.

AIKMAN, Rochester, N. Y.

SOME NOTES ON OFFICIAL STATISTICS OF SPEECH DISORDERS ENCOUNTERED DURING WORLD WAR I. RAYMOND CARHART, J. Speech Disorders **8**:97 (June) 1943.

The author summarizes the official statistics on the incidence of speech defects among enlisted personnel in the first World War and describes the rehabilitative work done at Cape May. PALMER, Wichita, Kan.

SPEECH SOUND ELEMENTS DURING THE FIRST YEAR OF LIFE: A REVIEW OF THE LITERATURE. ORVIS C. IRWIN and HAN PIAO CHEN, J. Speech Disorders **8**:109 (June) 1943.

Irwin and Chen review the literature relative to the development of speech sounds in infants during the first year of life. Various methods of studying the development of the function are discussed. The statistical approach has not been fully exploited in work on infants' speech. PALMER, Wichita, Kan.

A PHONOGRAPHIC SCALE FOR THE MEASUREMENT OF DEFECTIVE ARTICULATION. ROBERT CURRY, LOU KENNEDY, LORETTA WAGNER and WALTER WILKE, J. Speech Disorders **8**:123 (June) 1943.

A selection containing all the sounds used in English and most of the consonant blends was read by 8 children whose speech varied from completely unintelligible to normal, and recordings were studied by 10 adults. Deficiencies in the experiment were corrected in a second series, of 10 recorded samples judged by 131 to 192 observers. These recordings were ranked to form a scale which can be used to measure the intelligibility of a person's speech and the seriousness of any articulatory defect by comparison with the phonographic samples. PALMER, Wichita, Kan.

A STUDY OF SOUND DISCRIMINATION ABILITY OF ELEMENTARY SCHOOL PUPILS. MILDRED TEMPLIN, J. Speech Disorders **8**:127 (June) 1943.

Thirty elementary school pupils in grades 2 to 6 were given two tests, each with 100 consonant items, identical except for the position of the consonant element or combination. In the first test, the consonant was in the initial position, and in the second, in the final position. The children made more errors in discrimination between the consonants which were in the middle or final position, than between those which were initial. Such a short test is effective and statistically reliable.

PALMER, Wichita, Kan.

A NOTE ON VOICE RECORDINGS. ERNEST H. HENRIKSON, J. Speech Disorders **8**:133 (June) 1943.

In nearly half of the cases in this study, there was no change in judgment of his own speech by the person tested after he heard a recording of it. Some subjects moved closer to the observers' ratings, and some moved farther from these evaluations. The four trained judges did not agree in more than 20 per cent of the cases for pitch, 56 per cent for rate and 48 per cent for loudness. It is apparent that even experienced persons make errors in the evaluation of these three factors in speech. PALMER, Wichita, Kan.

A CARDIOVASCULAR AND METABOLIC STUDY OF STUTTERERS AND NON-STUTTERERS. C. H. RITZMAN, J. Speech Disorders **8**:161 (June) 1943.

In a study of 29 stutterers at the University of Iowa, Ritzman was unable to replicate most of Palmer's and Gillette's results. No significant differences were found for heart rate, but the study tended to confirm the previous observation that women who stutter have less marked sinus arrhythmia than those who do not. The author believes that such studies are of more value if the divergences from normal are interpreted as the physiologic consequences of stuttering rather than as etiologic factors. PALMER, Wichita, Kan.

ACUTE LARYNGOTRACHEOBRONCHITIS: TREATMENT OF THE OBSTRUCTIVE LARYNGEAL AND TRACHEOBRONCHIAL EDEMA WITH HYPERTONIC HUMAN PLASMA: A PRELIMINARY REPORT. HARRY L. BAUM, Laryngoscope **53**:371 (June) 1943.

Acute laryngotracheobronchitis often produces death by the inflammatory edema of the subglottic tisues. The violent respiratory effort causes secondary myocardial failure. Tracheotomy reduces the mortality only about 50 per cent and is in itself a somewhat hazardous procedure. After it there may be further changes in the bronchi resulting in asphyxia, atelectasis and pneumonia.

Concentrated plasma has been effective in other edematous conditions, including cerebral and nephrotic edema. It is also effective in reducing the subglottic edema of acute laryngotracheobronchitis. This it accomplishes by its high concentration and resultant osmotic action. Such action withdraws fluid from the tissues into the blood stream. It is in no way curative for the infection. It only reduces the edema.

Particularly to prevent overloading of the circulation, preliminary venesection is of value. Blood is removed to a volume three to four times that of concentrated plasma introduced into the veins. The concentration of the plasma should be approximately four times its usual strength. This is accomplished by diluting dried plasma with one quarter of the usual amount of water. This procedure is valuable also for the tracheotomized patient, for it prevents subsequent edema. From 24 to 40 cc. of the concentrated plasma is injected, depending on the size of the child. Few reactions are encountered, and these are not severe. If the vein is prepared so that a stylet can be left in it, subsequent injections can be easily administered if necessary. Results are almost immediate. The breathing becomes quiet and the color is restored. It is to be noted again that the obstruction only is relieved and that the infection has not been cured.

The author suggests other conditions with edema in which this method can be applied. He points out that his own experience has been limited to comparatively few cases. He hopes that physicians interested in the subject will give the method a more extended trial in order that its value may be determined more accurately.

HITSCHLER, Philadelphia. [ARCH. OTOLARYNG.]

## Diseases of Lungs, Pleura and Mediastinum

ASTHMA IN CHILDHOOD. ARTHUR HURST, Brit. M. J. **1**:403 (April 3) 1943.

This publication is an opening address to the Section of the Study of Disease of Children of the Royal Society of Medicine and does not lend itself to abstracting. Its worth can be obtained only by reading the entire article. BIRDSONG, Charlottesville, Va.

CHRONIC LUNG DISEASE IN CHILDHOOD. C. W. VINING, Practitioner **150**:205 (April) 1943.

The author lists as the causes of chronic cough in children catarrhal infections of the upper respiratory tract, whooping cough, unhealthy states of the nasopharynx and nervousness. He discusses at some length the role of tuberculosis and of the chronic nontuberculous diseases of the chest such as collapse of the lungs, bronchial pneumonia, asthma, empyema and a few rarer conditions.

Postural drainage, remedial exercises, surgical intervention and the more obvious treatment, such as clearing infections, treating asthma and balancing the nutritional requirements of the patient, are discussed.

THELANDER, San Francisco.

PNEUMATOCELE, OR LOCALIZED BULLOUS EMPHYSEMA FOLLOWING PNEUMONIA. P. BARCLAY, Proc. Roy. Soc. Med. **36**:380 (May) 1943.

Pneumatocele in a baby 8 months old is reported. Pneumonia which developed when the child was 6 months old was successfully treated with sulfapyridine. Ten days after the onset of pneumonia a roentgenogram of the chest showed two small opacities at the base of the right lung. At this time the child had severe gastroenteritis, and he remained extremely ill for six weeks. During this period a series of roentgenograms were obtained which showed the development of air-filled spaces in the right pulmonary field. One of these spaces increased greatly in size and then became rapidly smaller and finally disappeared entirely. The baby had few symptoms referable to the condition in the chest. The signs in the chest were those of bronchitis with scattered rales. The author discusses the possible causes of such a condition. WILLIAMSON, New Orleans.

## Diseases of the Gastrointestinal Tract, Liver and Peritoneum

CREAM-FILLED PASTRY SOURCE OF INFECTION. Health News **20**:108 (June 28) 1943.

Twenty cases of severe gastroenteritis which occurred in the state of New York were traced to cream-filled cakes which showed Staphylococcus aureus.

AIKMAN, Rochester, N. Y.

STUDIES OF THE ACUTE DIARRHEAL DISEASES: CULTURAL OBSERVATIONS ON THE RELATIVE EFFICACY OF SULFONAMIDES IN SHIGELLA DYSENTERIAE INFECTIONS. ALBERT V. HARDY, WILLIAM BURNS and THELMA DECAPITO, Pub. Health Rep. **58**:689 (April 30) 1943.

Of the sulfonamide drugs tested, sulfadiazine stood first in rapidity of action, and it was judged the most promising for the treatment of clinical infections due to the varieties of Shigella encountered in this country. Succinylsulfathiazole was more in general effective than sulfaguanadine and was superior even to sulfadiazine in the treatment of convalescent and passive carriers of the Sonne strain. SANFORD, Chicago.

STUDIES OF THE ACUTE DIARRHEAL DISEASES: TYPING OF SHIGELLA DYSINTERIAE FLEXNER. ALBERT V. HARDY, JAMES WATT and THELMA DECAPITO, Pub. Health Rep. **58**:696 (April 30) 1943.

The authors describe an agglutination procedure that they have used for the last five years, a modification of that of Andrewes and Inman. Antiserums of Flexner types V, W, X and Z are used. The authors regard this method as much simpler than the agglutination-absorption test and as of greater epidemiologic value. SANFORD, Chicago.

FIBROUS STRICTURE OF GULLET OF NINETEEN YEARS' DURATION. G. GREY TURNER, Brit. J. Surg. **30**:344 (April) 1943.

An esophageal stricture developed in a 7 year old boy who had swallowed sodium hydroxide. Several unsuccessful attempts were made to dilate the stricture and to create an antethoracic esophagus. During the following nineteen years the patient was fed through a rubber antethoracic esophagus connecting an esophageal fistula and a gastrostomy opening. A complicating gastric ulcer developed on the posterior wall of the lesser curvature. Nineteen years after development of the stricture Turner restored normal swallowing by bougienage, beginning treatment with a no. 6 esophageal bougie (4 mm.). Two years after bougienage was begun, with the esophagostomy and gastrostomy fistulas closed, the patient was able to pass a no. 16 bougie with ease, although he had not passed a bougie for six months. BRICK, Toronto, Canada.

SULPHAGUANIDINE IN NEONATAL EPIDEMIC GASTRO-ENTERITIS. J. L. HENDERSON, Brit. M. J. **1**:410 (April 3) 1943.

Six epidemics and a few sporadic cases comprising a total of 102 cases of gastroenteritis occurred in the Simpson Maternity Hospital, Edinburgh, Scotland, in the three year period from 1940 to 1942. At no time was any definite etiologic factor established in these cases. The incidence of gastroenteritis was much higher in premature infants than in mature babies. Practically all of these babies were bottle-fed children. Seventy-two are classified by the author as untreated and 30 as treated. The untreated patients, who served as the controls, were observed during 1940, 1941 and part of 1942. The treated patients were seen in the latter part of 1942. Therefore, this is not a fairly controlled experiment.

The treatment of the two groups was practically the same, except that to the so-called treated patients sulfaguanidine was administered in fairly large amounts. To mature infants 0.75 Gm. of sulfaguanidine was given as an initial dose and 0.5 Gm. every succeeding four hours. For premature infants the initial dose was 0.5 Gm., with 0.25 Gm. every three hours thereafter. The author states that children tolerate these high doses well and that it is important that they be given doses in this range. The other treatment consisted of entirely withholding milk and substituting lactose or dextrimaltose every one and one-half hours. Four ounces of fluid per pound of birth weight is needed every twenty-four hours; if this quantity is not taken by the infant feeding by gavage is necessary. With this method the parenteral administration of fluid is rarely necessary. The author stresses that milk should not be introduced into the diet until the patient shows considerable improvement and the feedings are taken with some eagerness. He has no apprehension at all over withholding milk for as long as a week from these small infants. The mortality for the untreated patients was 70, 86 and 69 per cent for the years 1940, 1941 and 1942, respectively. For the 30 treated patients the mortality was 10 per cent. The author states that 4 deaths of treated patients were eliminated from the data because treatment was not started until the fourth

day of the disease and because sulfaguanidine was not given in large enough doses. However, including these 4 deaths the mortality would be only about 23 per cent.

BIRDSONG, Charlottesville, Va.

NECROSIS OF ISLETS OF LANGERHANS PRODUCED EXPERIMENTALLY. J. SHAW DUNN, H. L. SHEEHAN and N. G. B. MCLETCHIE, Lancet **1**:484 (April 17) 1943.

Acute necrosis of almost all the islet tissue of the pancreas has been observed in rabbits after intraperitoneal inoculation with a synthetic styryl quinoline (2[p-acetylaminostyryl] 6-dimethylaminoquinoline methochloride) and after intravenous inoculation with alloxan (the ureide of mesoxalic acid). The development of this lesion is accompanied by an initial rise of blood sugar, followed by an intense hypoglycemia, which ends fatally with subnormal temperature in twelve to forty-eight hours. It is suggested that the lesion may be caused by overstimulation of the islets with excessive production of insulin and later death of the cells from overstrain.

The adrenal cortex and the thymus in some of the animals showed congestion and petechial hemorrhages, while minor cytologic changes were observed in a histologic study of the thyroid. LANGMANN, New York.

REVIEW OF THE CASES OF COELIAC DISEASE IN A HOSPITAL FOR SICK CHILDREN SINCE THE OUTBREAK OF WAR. ELEANOR K. PECK, Proc. Roy. Soc. Med. **36**:379 (May) 1943.

Celiac disease appears to be on the increase since the beginning of the war. There may be many contributory factors, such as the closing down of some hospitals, various shifts of the juvenile population, the scarcity of general practitioners and possibly an actual increase in the evidence of the disease under the present nutritional state of the country. From a comparison of recent and prewar records at the hospital (Great Ormond Street) it appeared that the incidence had increased sixfold during the war. The age of the patient when first seen was, on the average, 2 years. The majority of the patients had clearly apparent signs of the disease, but a few of the more recent patients were picked up before wasting had become evident. One or more determinations of the amount of fat in the feces were made for each patient. The treatment employed was the use of a fat-free or low fat diet with various extracts of liver. The addition to the diet of supplementary vitamins and iron and an occasional transfusion played an important part. Observations made by May, McCreary and Blackfan recently suggest that celiac disease is due to a deficiency of one or more undetermined factors of the vitamin B complex. If this is so there may possibly be an increase in the disease under the nutritional conditions resulting from the war.

WILLIAMSON, New Orleans.

CRUVEILHIER-BAUMGARTEN SYNDROME IN AN INFANT. AGUSTIN CASTELLANOS, Arch. de med. inf. **13**:86 (April-June) 1943.

Icterus, hepatomegaly, splenomegaly, collateral venous circulation and protruding umbilicus occurred in a white boy aged 22 months. This syndrome is found in various cirrhoses of the liver and in syphilitic hepatitis. Although the reactions to serologic tests were negative, the child improved under treatment with mercurial compounds.

SANFORD, Chicago.

## Nervous Diseases

SEQUELS OF EQUINE ENCEPHALOMYELITIS. H. H. NORAN and A. B. BAKER, Arch. Neurol. & Psychiat. **49**:398 (March) 1943.

Neurologic sequels of a chronic and progressive nature may follow attacks of equine encephalomyelitis.

A clinicopathologic study of a case of equine encephalomyelitis revealed a destructive process which had produced multiple glia-lined cavities within the frontal lobes and widespread degeneration of the parenchymal elements throughout the brain. Many of the blood vessels were occluded. This extensive damage suggested a vascular spread of the virus.

BEVERLY, Chicago.

JUVENILE AMAUROTIC IDIOCY. ALBERT J. LUBIN and OTTO MARBURG, Arch. Neurol. & Psychiat. **49**:559 (April) 1943.

A case of juvenile amaurotic familial idiocy is described. An attempt is made to correlate the results of neurologic, psychologic, encephalographic and histologic studies, with particular reference to cortical activity. In spite of severe and widespread cellular alterations, cortical functions were retained, and the electroencephalographic pattern was not especially impaired.

BEVERLY, Chicago.

OPTOCHIASMIC ARACHNOIDITIS. EDWARD R. RYAN, Arch. Ophth. **29**:818 (May) 1943.

Ryan reports 3 cases of chiasmic arachnoiditis, confirmed at operation, in which the symptoms were different.

Of the 3 cases, the first offered a difficult problem in diagnosis. The case was that of a 7 year old boy with but one complaint—progressive impairment of vision for two years. The bilateral central scotomas and the atrophy of the optic nerves were accompanied by roentgenographic evidence of destruction of bone in the posterior wall of the right orbital canal, with a normal sella turcica. Operation did not improve the patient's visual acuity.

The second case was that of a 9 year old boy whose only complaint was poor vision in the right eye for three months, with rapid progression of the process during the month before examination. The only signs were papilledema in the right eye, with extensive depression of the visual field in that eye, more advanced in the temporal half, and pronounced depression of the field in the left eye. The diagnosis was confirmed surgically. After operation the fields of vision widened to a notable degree, and vision in the right eye improved from 0.1, prior to operation, to 0.4, after operation; in the left eye vision after operation was slightly less than that present before surgical intervention. Secondary atrophy of the optic nerve became established after the operation.

In the third case, that of a man aged 34, examination showed normal fundi with bitemporal field defects, more pronounced on the right side. The sella was normal, but the optic foramens were pathologic. The right optic foramen measured 5 by 6 mm. and its margins were decalcified; the left optic foramen measured 4.5 by 4.5 mm., and the margins were clear. After operation and confirmation of the diagnosis, the fields showed an enormous expansion on both sides.

SPAETH, Philadelphia.

[ARCH. NEUROL. & PSYCHIAT.]

CONGENITAL PARALYSIS OF LATERAL ROTATORS OF EYES WITH PARALYSIS OF MUSCLES OF FACE. AVERY M. HICKS, Arch. Ophth. **30**:38 (July) 1943.

Congenital bilateral paralysis of the muscles which move the eyes in the horizontal plane and congenital bilateral paralysis of the muscles of the face occasionally occur together. This disabling congenital anomaly makes up a small group of congenital defects which probably form a step in the transition between certain forms of congenital absence of abduction and the congenital ophthalmoplegias. Various authors have described this condition from time to time, with an occasional pathologic report showing hypoplasia of the brain stem in the area of the sixth and seventh cranial nerves.

This combination of paralysis of the lateral rotators and both abductors and adductors with normal vertical movements of the eyeballs, but with disturbances in the function of the muscles of the face, is frequently spoken of as the Möbius syndrome. It was first described by him, in 1888 and again in 1892.

Hicks reports 4 cases of this syndrome and reviews the theories responsible for the condition.

The exact nature and site of the lesions which produce the Möbius syndrome are not known. It is probable that the site, nature and extent of the lesion are different in various cases. In cases in which nystagmus is absent on vestibular stimulation and there is a response of the internal rectus muscle to impulses of convergence but not to impulses for associated movements, as in case 3 of the author's series, the lesion probably interferes with the continuity of the fibers of the posterior longitudinal fasciculus, so as to prevent the impulses originating in the vestibular apparatus from reaching the nucleus of the third nerve. This nucleus and the fibers to the internal rectus muscle must be intact; otherwise, convergence would be impossible. The lesion is probably at the level of the nuclei of the sixth and seventh cranial nerves, but may extend above and below the level of these centers. In case 4, that of a boy with poor convergence and weakness of the upward and downward rotations, the disease process had probably extended upward to involve a portion of the nucleus of the third nerve.

Several theories have been advanced to account for the nature of the disease process which produces this clinical picture. The best known are Möbius' theory of intrauterine nuclear disease, Kann's theory of congenital aplasia of part of the brain stem and Hübner's theory of hypoplasia of the brain stem. Hübner based his theory of hypoplasia on the anatomic examination of the brain stem of a 19 month old boy who showed complete bilateral absence of abduction with paralysis of the muscles of the face. The involvement of the facial musculature was more pronounced on the left side, and there was atrophy of the left half of the tongue. Postmortem examination disclosed marked defects in the motor ganglions and nerve fibers in the medulla and the pons. There were practically no cells in the nuclei of the facial, hypoglossal and abducens nerves. There were no signs of degeneration or inflammation, and Hübner concluded, therefore, that the defect was due to hypoplasia. The clinical phenomena offer no basis on which to judge the value of the various theories; in fact, it is not possible to determine whether the anatomic anomalies observed in the muscles represent primary or secondary changes. Thus, one must conclude that this congenital anomaly is due to a pathologic process of an unknown nature involving the brain stem.

SPAETH, Philadelphia.
[ARCH. NEUROL. & PSYCHIAT.]

A CASE OF CEREBELLAR ATROPHY. MOGENS ELLERMANN, J. Nerv. & Ment. Dis. **97**:389 (April) 1943.

Ellermann reports the case of a man aged 65 who, at the age of 4½ years, had sustained a severe injury to the head, followed by behavior difficulties and failure of mental development. Between the ages of 35 and 40 signs of cerebellar disease gradually appeared, with ataxic gait, intention tremor and dysarthria. At about the age of 44 he was hospitalized with an atypical and grandiose type of psychosis, later marked by psychic dissolution. Pneumoencephalographic examination revealed pronounced cerebellar atrophy. In view of the late development of the cerebellar syndrome, a traumatic origin was considered unlikely. Because of the purity of the cerebellar picture, the case is classed as one of abiotrophy, probably a primary parenchymatous atrophy of the cortex of the type first described by Marie, Foix and Alajouanine.

CHODOFF, Langley Field, Va.
[ARCH. NEUROL. & PSYCHIAT.]

INTRACRANIAL ANEURYSMS. MAX H. WEINBERG, J. Nerv. & Ment. Dis. **97**:666 (June) 1943.

Weinberg reports 3 cases of intracranial aneurysm, with special emphasis on the individual symptoms. The first case was that of a boy aged 12 years who suddenly became faint while playing and quickly exhibited signs of meningeal irritation, with bloody spinal fluid. During apparent recovery he relapsed, had a convulsive seizure and died. Autopsy revealed a necrotic cavity, containing blood, in the left frontal lobe. An insignificant branch of the left anterior communicating artery was apparently the site of the aneurysm. In the second case, headache which had been present for years cleared up entirely after the patient recovered from the effects of the rupture of an aneurysm. The third case was that of a man aged 67 with complaints of headache and increasing lethargy. A roentgenogram of the skull revealed calcification in the walls of the internal carotid artery with some aneurysmal dilatation, and it was thought that this was responsible for the symptoms.

CHODOFF, Langley Field, Va.
[ARCH. NEUROL. & PSYCHIAT.]

WESTERN EQUINE ENCEPHALOMYELITIS IN INFANTS. HARRY MEDOVY, J. Pediat. **22**:308 (March) 1943.

Seventeen cases of western equine encephalomyelitis occurring in infants under the age of 1 year are presented. Twelve of the patients recovered completely, and 5 had sequelae in the form of mental retardation and spasticity. Characteristic clinical symptoms were fever, persistent convulsions, bulging fontanels, a severe lead pipe type of rigidity with opisthotonos, and increased globulin and pleocytosis in the spinal fluid. The final diagnosis was confirmed by complement fixation tests of the blood for the virus of western equine encephalomyelitis. Of considerable interest were 2 patients, aged 6 and 7 months, who were spastic and had mental retardation and whose blood when routinely tested gave positive complement fixation. History revealed in both instances an acute cerebral episode with fever, occurring four and five days after birth, during August, at the time of the epidemic. At that time the mothers also were ill; 1 had a condition diagnosed as an infection of the respiratory tract and the other had a paralysis which was diagnosed as poliomyelitis. Their blood was also found to give positive complement fixation for the virus. Thus, a prenatal transfer of the virus seems likely. Incidentally, blood taken from mothers of the other babies with encephalo-

myelitis reacted negatively in the complement fixation tests. The author suggests encephalomyelitis as a cause in some cases of spasticity in infants.

STETTENBENZ, Buffalo.

ON SOME ANOMALOUS FORMS OF AMAUROTIC IDIOCY AND THEIR BEARING ON THE RELATIONSHIP OF THE VARIOUS TYPES. R. WYBURN-MASON, Brit. J. Ophth. **27**:145 (April); 193 (May) 1943.

Wyburn-Mason reports a group of cases of amaurotic idiocy of the type described by Tay, in some of which there were atypical features. This is followed by a group of cases of the juvenile type; in some of these the disease was of the late infantile type described by Bielschowsky under the term "late infantile familial amaurotic idiocy with cerebellar symptoms." Still another group comprises instances of the late juvenile type. Finally, an adult type is described.

Evidence is brought forward that there are two types of the disease, infantile and juvenile, which are not related to one another except in their similar histologic appearances. It is probable that atypical forms of the juvenile disease occur in which either the retinal or the cerebral manifestations are absent, especially in older patients. It seems likely that the disease is unrelated to macular heredodegeneration.

The article is illustrated with drawings of fundi.

W. ZENTMAYER, Philadelphia. [ARCH. OPHTH.]

DISCUSSION ON RECENT EXPERIENCES OF ACUTE ENCEPHALOMYELITIS AND ALLIED CONDITIONS. Proc. Roy. Soc. Med. **36**:319 (April) 1943.

Dr. Russell Brain stated that in two years he had observed 22 cases of acute encephalitis. In 6 the onset was acute or even fulminating, with high fever and stupor or coma; in 3 of these there were signs of meningitis. In spite of a stormy onset of the disease, 5 persons recovered completely. In 2 cases the onset was subacute and the course progressed to death in a few months. In 3, the onset was subacute and the course at first relapsing. From these cases he concluded that there seem to be three different patterns of reaction of the nervous system to infection.

Dr. Brain outlined seven types of infection causing encephalomyelitis:

1. Meningoencephalitis due to pyogenic organisms. This may be either meningococcic encephalitis or meningoencephalitis complicating scarlet fever.

2. Encephalitis with intranuclear inclusion bodies. During recent years several new forms of encephalitis due to virus infection have been discovered, such as Japanese B encephalitis and St. Louis encephalitis, the characteristic feature being the presence of eosinophilic inclusion bodies in the nuclei of the cortical ganglion cells. The author described a case of this form in a boy of 11 years.

3. Encephalitis due to viscerotropic viruses.

4. Acute aseptic meningitis.

5. Postexanthematous encephalitis.

6. Neurologic sequelae of inoculation with toxoids or killed bacteria. These manifestations may follow inoculation with tetanus toxoid, typhoid-paratyphoid-paratyphoid B vaccine or diphtheria toxoid.

7. Sulfanilamide encephalopathy.

J. G. Greenfield and Dorothy Russell described the pathologic conditions observed in encephalitis.

WILLIAMSON, New Orleans.

## Psychology and Psychiatry

CHARACTER EDUCATION IN CHILDHOOD AND YOUTH. VERNON JONES, Bol. Inst. internac. am. de protec. a la infancia **16**:556 (April) 1943.

The author develops the theory that real character does not consist in conforming to the accepted standard of morals and good conduct but is a dynamic constructive force which should center not in the individual but in his relation to society. He discusses various methods of attempting to achieve such character development in education. He favors what he calls the direct-indirect method, in which there is definite planning on the part of the teacher but in which "the learner has his attention directed not to improvement in character but rather to activities involving actual choices in the area of character and citizenship" (page 464). Additional value seems to be derived from discussion in planning the activity and discussion of its significance after completion.

Methods of cooperation between school and church and between school and home are discussed. Finally it is emphasized that "the teacher—all that he is and stands for—is the keystone in whatever structure of character education is built" (page 474).

LESLIE, Evanston, Ill.

## Diseases of the Genitourinary Tract

ACUTE NEPHRITIS AND THE EFFECT OF SULFONAMIDES ON THE KIDNEYS. FRANCIS D. MURPHY and WILBUR D. WOOD, Ann. Int. Med. **23**:999 (June) 1943.

Sulfonamide compounds may effect cures in some cases of acute glomerulonephritis, but in other instances the use of these drugs may cause damage to the kidneys. Alkalinization of the urine and the free use of fluids will minimize the dangers of the formation of sulfonamide crystals in the ureters and tubules.

READING, Galveston, Texas.

DIODRAST AND INULIN CLEARANCES IN NEPHROTIC CHILDREN WITH SUPERNORMAL UREA CLEARANCES. KENDALL EMERSON JR. and VINCENT P. DOLE, J. Clin. Investigation **22**:447 (May) 1943.

The elevated urea clearance in 4 nephrotic children was found to be associated with increase of both inulin and diodrast clearances. [AUTHORS' SUMMARY.]

FATAL ANURIA FOLLOWING ADMINISTRATION OF SULFONAMIDES WITH REFERENCE TO TUBULAR NECROSIS AND REGENERATION. J. A. ERGANIAN and JOHN H. DOVAL, J. Lab. & Clin. Med. **28**:808 (April) 1943.

A case of fatal anuria in a 9 month old boy following the administration of sulfathiazole is reported. Among the pathologic conditions observed was a necrosis of the renal epithelium, with early regeneration. The authors point out the greater importance of this condition as compared with the usually emphasized formation of obstructive concrements in the ureters and tubules.

WILKINSON, Galveston, Texas.

A POSSIBLE CURE FOR ENURESIS. ROBERT BOYD, M. Rec. **156**:216 (April) 1943.

The author suggests the use of fluidextract of ergot in the treatment of enuresis and reports 1 case in which it was successful.

FERDINAND, Peoria, Ill.

THE PHYSIOLOGY OF CHRONIC NEPHRITIS. J. M. HAYMAN JR., M. J. Australia **1**:291 (April 3) 1943.

"Chronic Bright's disease (chronic glomerulonephritis and arteriolar nephrosclerosis) is characterized by a reduction in the number of kidney units or nephrons. Large numbers of destroyed glomeruli may completely disappear without leaving recognizable scars.

"Kidney function, as measured by the urea clearance test or maximum specific gravity test, correlates better with the number of remaining nephrons than it does with kidney weight.

"Dogs rendered hyposthenuric by subtotal nephrectomy will excrete urine of normally high specific gravity when the concentration of the plasma proteins is increased, or when systolic blood pressure is reduced to the level at which urine is just being formed.

"While the possibility of qualitative change in the remaining tubular epithelium in chronic nephritis cannot be excluded, it seems probable that the characteristic increased volume of dilute urine may be in the nature of a flood diuresis through a small number of nephrons, mediated through changes in the composition of the blood, in the calibre of vessels or in blood flow."

AUTHOR'S SUMMARY.

PHIMOSIS IN INFANCY. ANTONIO CARBONELL SALAZAR, Pediat. Américas **1**:331, 1943.

A short paper is presented on the types and treatment of phimosis in infancy. The condition may be acquired or congenital. If adhesions exist between the glans and the foreskin the author calls it "false phimosis." The treatment is to force the skin back over the glans and after careful cleansing to paint the glans with liquid petrolatum. The skin is then returned over the glans. This maneuver may have to be repeated in five to seven days. Atrophic phimosis is defined as narrowing of the preputial orifice. The treatment consists in stretching the orifice with a forceps by inserting it closed and then gently opening it. Surgical treatment is deprecated. Three methods exist: simple incision, circumcision and a combination of the two. Salazar condemns prophylactic circumcision.

ZETTELMAN, Evanston, Ill.

## Diseases of the Ductless Glands; Endocrinology

A REVIEW OF ADRENAL CORTICAL HYPERTROPHY, JAY TEPPERMAN, FRANK L. ENGEL and C. N. H. LONG, Endocrinology **32**:373 (May) 1943.

After reviewing the literature the authors classify the well authenticated conditions in which adrenal hypertrophy has been described in the following manner:

I. Primary increase in anterior pituitary adrenotropic hormone or administration of adrenotropically active pituitary extracts.

II. Secondary increase in anterior pituitary adrenotropic hormone.

1. Compensatory hypertrophy.
   - A. After unilateral adrenalectomy or bilateral enucleation.
   - B. By the parabiotic effect from an adrenalectomized animal or an intact animal.
   - C. By the vicarious action of fetal adrenal glands.
2. Estrogen treatment.
3. Absolute increase in requirement of adrenal cortical hormone.
   - A. Increase in products of endogenous protein catabolism.
     - a. Secondary to hypermetabolism induced by administration of thyroxin, cold, exercise, puerperium and lactation or deficiency in magnesium.
     - b. From an obligatory increase in protein catabolism in relative carbohydrate deprivation due to starvation, phlorhizin diabetes or treatment with insulin.
     - c. Secondary to other causes such as hemorrhagic and traumatic shock, burns, anoxia, infection, toxemia or thiamine deficiency.
   - B. Increase in products of exogenous protein catabolism due to a high protein diet.

A hypothetic mechanism for adrenal hypertrophy may be summarized in the following manner. The adrenal cortical hormone may inhibit the adrenotropic activity of the anterior lobe of the pituitary gland, and the adrenotropic secretion may therefore increase if the concentration of cortical hormone in the body fluid falls. Such a fall in the concentration of cortical hormone may be brought about by an increase in the rate of inactivation (utilization) of the hormone which is a function of the hormone requirement of the organism. The requirement of cortical hormone may be increased by the presence in the body of excessive amounts of a substrate which requires the presence of the hormone for its catabolism. It is possible to conceive of this substance as mobilizing cortical hormone either by way of the end organ in which it is catabolized or by direct action on the adrenal cortex. Finally, it is suggested that this substrate may be derived from the animal's own tissues (as in various stresses) or from dietary protein.

JACOBSEN, Buffalo.

EFFECT OF HIGH PROTEIN DIETS ON SIZE AND ACTIVITY OF THE ADRENAL CORTEX IN THE ALBINO RAT. JAY TEPPERMAN, FRANK L. ENGEL and C. N. H. LONG, Endocrinology **32**:403 (May) 1943.

Two groups of rats were fed on high protein and high carbohydrate diets respectively. The rats in the group receiving a high protein diet showed a 40 to 50 per cent increase in the size of the adrenal glands. Saline extract of the anterior lobe of the pituitary gland greatly increased the size of the adrenal glands in both groups over that achieved by diet alone.

On the basis of the survey of the literature and the experimental data on animals receiving high protein diets, it is suggested that some event or series of events occurring during the catabolism of protein may serve as a stimulus for the hypertrophy of the adrenal cortex observed in a variety of circumstances.

JACOBSEN, Buffalo.

EFFECT OF DIET IN RATS ON ADRENAL WEIGHTS AND ON SURVIVAL FOLLOWING ADRENALECTOMY. DWIGHT J. INGLE, GORDON B. GINTHER and JAMES NEZAMIS, Endocrinology **32**:410 (May) 1943.

A study was made of the effect of different proportions of carbohydrate, protein and fat in diet on the weights of the adrenal glands of rats and on the periods of survival after adrenalectomy. The observed differences were small and probably without significance.

JACOBSEN, Buffalo.

OBSERVATIONS ON THE RELATIONSHIP OF THE THYROID TO THE POLYURIA OF EXPERIMENTAL DIABETES INSIPIDUS. C. E. RADCLIFFE, Endocrinology **32**:415 (May) 1943.

In cats with well established diabetes insipidus due to lesions of the hypothalamic-hypophysial system, dietary administration of thyroid tissue produces an increased urinary output which is associated with a positive shift in the chloride balance, that is, a diminished output of chlorides. JACOBSEN, Buffalo.

ADRENOCORTICAL-LIKE TISSUE IN THE OVARIES OF THE ADRENALECTOMIZED GROUND SQUIRREL (CITELLUS TRIDECEMLINEATUS). RICHARD A. GROAT, Endocrinology **32**:488 (June) 1943.

The ovaries in a female ground squirrel which has undergone adrenalectomy invariably become the site of formation of adrenocortical-like tissue. The process is principally one of metaplasia and does not occur in the absence of the hypophysis. JACOBSEN, Buffalo.

DETERMINATION OF THE RATE OF THYROID HORMONE SECRETION AT VARIOUS ENVIRONMENTAL TEMPERATURES. E. W. DEMPSEY and E. B. ASTWOOD, Endocrinology **32**:509 (June) 1943.

There are many observations which suggest that the thyroid gland secretes its active principle more rapidly in cold than in warm environments. It is a noteworthy fact, however, that this conclusion is based on indirect evidence, from which only qualitative estimates of increased or decreased activity could be made. The possibility of obtaining quantitative information has been suggested by recently published observations on the mode of action of antithyroid compounds such as thiouracil.

Growth is inhibited and cretinous types produced when thiouracil is administered to very young animals. The formation of thyroid hormone in rats was prevented by administration of one of the antithyroid drugs (2-thiouracil). Simultaneously, thyroxin, in measured quantities, was administered. At the end of an adequate period, the thyroid was removed and weighed. By plotting the weight of the thyroid gland against the quantity of thyroxin administered, the thyroxin requirement for maintenance of the gland at a normal weight, despite the antithyroid drug, was determined. This value, it is considered, is equivalent to the rate of production of thyroid hormone in normal animals maintained under the conditions of the experiment.

The rate of enlargement of the thyroid gland in response to administration of thiouracil was low in animals kept in hot environments and high in rats maintained in the cold. A quantity of thyroid hormone equivalent to 5.2 micrograms of thyroxin daily was required to maintain a thyroid of normal weight in young male rats kept at room temperatures averaging 25 C. At 1 C. the requirement of thyroxin was increased to 9.5 micrograms, while at 35 C. it was decreased to 1.7 micrograms. These values are considered to be equivalent to the amounts of hormone produced by the normal thyroid gland under these conditions.

JACOBSEN, Buffalo.

THE EFFECT OF CHLORIDE WITH HIGH AND LOW IODINE SUPPLY ON THE THYROID GLAND OF THE RAT. GEORGE R. SHARPLESS and E. KATHLEEN ANTHONY, J. Nutrition **25**:239 (March) 1943.

In rats, the concentration of iodine both in normal thyroid glands and in those deficient in iodine decreased with an excess of chloride in the diet. G. R. Sharpless and E. K. Anthony observed that a decrease in the intake of iodine produced enlargement of the thyroid glands in the rat, yet a reduction of the iodine concentration in the rat had no effect on the weight of the thyroid gland. FREDEEN, Kansas City, Mo.

SPORADIC CONGENITAL OBSTRUCTIVE GOITER WITH RECOVERY FOLLOWING OPERATION IN A THIRTEEN-DAY OLD INFANT. JOHN R. DAVIES, J. Pediat. **22**:570 (May) 1943.

Successful thyroidectomy was performed on a 13 day old boy who had an enlarged thyroid gland which produced symptoms of obstruction—stridor, dyspnea and cyanosis. The gland encircled the trachea and it was necessary to remove the portion lying posterior to the trachea as well as a large part of each lobe. Grossly and microscopically the appearance of the gland was identical with that in toxic diffuse goiter with hypothyroidism. Preoperative and postoperative therapy with iodine (sodium iodide and strong solution of iodine U. S. P.) was given to shrink the gland. Of considerable interest was the occurrence in the same family of an obstructive thyroid in one other boy who died thirteen days after birth and possibly in a third infant, also a boy, who died of an obstructive respiratory condition. This condition occurred in the three baby boys starting with the mother's fourth pregnancy, but a girl, the sixth child, escaped. The first three pregnancies resulted in normal full term boys.

The author stresses the value of lateral roentgenographic studies of the trachea in the diagnosis of cyanosis and dyspnea in infants when no cause can be determined otherwise, since visible swelling in the neck need not be present with an enlarged thyroid gland.

STETTENBENZ, Buffalo.

BILATERAL ADRENAL HEMORRHAGE. J. EDGAR MORISON, Lancet **1**:800 (June 26) 1943.

Three instances of sudden death of children with extensive hemorrhage into the adrenal glands are described. Two of the children were girls, each aged 4 months, and the third was a boy aged 3½ years.

Apart from the adrenal lesions these patients had widespread edema of the interstitial tissues and of the lungs, sequestration of red blood cells in dense aggregates in overdistended minute blood vessels and slight swelling of endothelial cells.

It is suggested that the structural changes found resulted from peripheral vascular failure, since they resembled those occurring in persons with surgical shock, and that they should be regarded as a consequence of bacterial toxemia and not of adrenal damage.

In addition to chemotherapy, treatment similar to that for post-traumatic shock should be given to patients with fulminant bacterial infections.

LANGMANN, New York.

## Diseases of the Muscles, Bones, Joints and Lymph Glands

EARLY OPERATION IN PREMATURE CRANIAL SYNOSTOSIS FOR THE PREVENTION OF BLINDNESS AND OTHER SEQUELAE. HAROLD K. FABER and EDWARD B. TOWNE, J. Pediat. **22**:286 (March) 1943.

Because of the unfavorable sequelae of premature synostosis of the cranial sutures, namely deformity of

the skull, and increased intracranial pressure followed by atrophy of the optic nerves, exophthalmos and mental deterioration, Faber and Towne feel justified in preventing it through linear craniectomy performed early in infancy. Five cases are presented in which the operation was performed. The follow-up of 4 patients has been long enough to demonstrate excellent results in appearance, development and mentality. The fifth child is still too young for appraisal.

Linear craniectomy with the excision of strips of bone along the fused suture lines was shown to allow almost immediate expansion of the skull, and this expansion, as demonstrated by tracings, continued for some time. Even though new bone formed in the excised areas, it was very thin and in some instances interrupted the continuity of the inner table of the skull, thus allowing expansion to occur, acting as a safety valve in preventing increased intracranial pressure.

The authors stress the early recognition of these cases, for in most instances the cranial deformity is apparent at or shortly after birth. Craniectomy should be performed before the age of 6 months, preferably at the age of 10 weeks. STETTENBENZ, Buffalo.

SERUM PHOSPHATASE VALUES IN CHILDREN SHOWING RETARDATION IN OSSEOUS DEVELOPMENT AND LOW METABOLIC RATES. A. MORGAN HILL and JEROME E. WEBBER, J. Pediat. **22**:325 (March) 1943.

The authors believe that more reliance can be placed on values for serum phosphatase as an aid in establishing the diagnosis of hypothyroid states than on values for serum cholesterol and for excretion of creatine. Twenty of 23 children with delayed osseous development and low basal metabolic rates had phosphatase levels of 5 to 6 Bodansky units or less. The range for 14 of 16 normal controls was 5 to 9.7 units, and the normal figure given by Bodansky is 7.5. It is admitted that the test is not 100 per cent diagnostic but must be used in correlation with observation of clinical signs and symptoms, determinations of the basal metabolic rate, roentgen studies of bones and determinations of cholesterol. STETTENBENZ, Buffalo.

## Skin Diseases; Allergy

ERYTHEMA INFECTIOSUM: REPORT OF AN EXTENSIVE EPIDEMIC. LOUIS CHARGIN, NATHAN SOBEL and HYMAN GOLDSTEIN, Arch. Dermat. & Syph. **47**: **467** (April) 1943.

An outbreak of erythema infectiosum, lasting from Nov. 4, 1941 to April 11, 1942, in an orphanage in the city of New York is reported. Eighty primary attacks and 90 relapses were observed.

The diagnosis of erythema infectiosum, according to the authors, is not difficult if the condition is once seen. The facial eruption is characteristic, showing symmetric erythema which resembles slapped cheeks. Further distinguishing features are the occurrence of the condition in epidemics, the mild general symptoms, the almost constant appearance of the rash first on the cheeks and often only there, the distribution, the distinct progression and evanescence of the rash, the lack of complications and the frequent relapses resulting in a long course.

A review of the literature shows that approximately fifty localized epidemics have been reported. Extensive laboratory and epidemiologic studies have failed to throw any light on the causation. In the public school attended by the affected children, not a single other case of the disease occurred. These facts suggest to the reviewer that a nutritional deficiency state may be associated with this condition. This possible relationship might be studied when another epidemic occurs.

JACKSON, Iowa City.

SENSITIZATION TO SULFONAMIDE COMPOUNDS. HERMAN SHARLIT, Arch. Dermat. & Syph. **47**:585 (April) 1943.

The author sent the following communication to the editor of *Archives of Dermatology and Syphilology:*

"The incidence of sensitization to sulfonamide compounds is great enough to warrant limitation of their use to treatment of diseases for which they are indispensable. Since the topical exhibition of these drugs readily leads to sensitization in persons who are susceptible dermatologists can do much to lessen unnecessary exposure to them.

"This is a plea for dermatologists not to cease experimenting with these drugs to seek out their value and place in their field of medicine but to refrain from using them for diseases that are common and for which effective therapy has long been available. I have in mind impetigo and pyoderma. By now, pharmaceutic manufacturers are recommending to members of the medical profession generally these drugs in ointment form for use against the aforementioned diseases. Would it be fair to deprive a patient of sulfonamide compounds for the treatment of pneumonia because previous use of such a drug in a salve for the treatment of impetigo had rendered him sensitive to and intolerant of them?" JACKSON, Iowa City.

ANTIBODIES TO HISTAMINE INDUCED IN HUMAN BEINGS BY HISTAMINE CONJUGATES. MILTON B. COHEN and HAROLD J. FREIDMAN, J. Allergy **14**:195 (March) 1943.

Histamine azoprotein was given to a group of patients with chronic urticaria, atopic dermatitis, contact dermatitis and vasomotor rhinitis of undetermined origin. The antigen was given in ascending doses, at intervals of three to seven days, over a period of from three months to a year.

"The experiments herein reported have demonstrated:

"1. Precipitins specific for histamine in sera of patients treated with histamine azo horse protein.

"2. In vitro neutralization of histamine by the sera of patients treated with histamine azo horse protein.

"3. In vivo neutralization of histamine as determined by iontophoretic skin tests on patients treated with histamine azo horse protein." HOYER, Cincinnati.

THE SOURCE OF THE ALLERGIC ACTIVITY OF HOUSE DUST. MARION T. DAVIDSON, J. Allergy **14**:244 (March) 1943.

The author feels that there is little reason to look beyond the self-evident substances which are present in houses and expect to find some unknown substance.

"House dust is composed of cotton, flax, jute, wool, silk, six or more animal hairs, three or more feathers, glue, kapok, orris root, pyrethrum, and tobacco."

In the discussion of the paper, Alan G. Cozart suggests that the antigen in house dust may be a product of the deterioration of cellulose (cotton and kapok).

HOYER, Cincinnati.

STUDIES ON THE BLOCKING ANTIBODY IN SERUM OF RAGWEED-TREATED PATIENTS: I. A SEARCH FOR INHIBITING SUBSTANCES IN OTHER TYPES OF IMMUNE SERUM. D. EDWARD FRANK and H. HAROLD GELFAND, J. Allergy **14**:273 (May) 1943.

The studies presented confirm the observations of others that treated pollen-sensitive serum does contain a specific blocking antibody, and that this antibody is not influenced in the test tube by the addition of convalescent serum containing other immune substances.

The skin of a patient who is cutaneously and clinically sensitive to pollen antigen does not alter its reaction because of previous inoculation with serums containing immune antibodies of the bacterial or virus type.

"The thermostable or blocking antibody is specific for each allergen and is not simulated immunologically by bacterial immune substances, either in vitro or in vivo."

HOYER, Cincinnati.

A COMPARISON OF THE SODIUM AND POTASSIUM METABOLISM OF ASTHMATIC AND NONALLERGIC CHILDREN. PAUL B. DONOVAN and GEORGE F. HARSH, J. Allergy **14**:281 (May) 1943.

The study was done on 12 children with asthma, and 10 children who were shown to be nonallergic. The two groups were comparable in age, size, race and sex, and lived under the same conditions. The diet contained potassium-rich foods supplemented by potassium chloride solution during the first, third and fifth weeks of the experiment. Sodium-rich foods and sodium chloride solution were given during the second and fourth weeks.

The study showed that:

"1. The asthmatic children ingested slightly more sodium than did the nonallergic children on both the high sodium and high potassium diets.

"2. The plasma potassium concentration of the asthmatic children on the high sodium diet was slightly higher than it was on the high potassium diet, and slightly higher than the plasma potassium concentration of the nonallergic children on either diet.

"3. The plasma sodium concentration of the asthmatic children on the high sodium diet was slightly lower than that of the nonallergic children despite a slightly greater intake.

"4. The asthmatic children excreted more sodium and more acid in the urine on both diets than did the nonallergic children."

HOYER, Cincinnati.

REPEATED BRONCHIAL RELAXATION IN THE TREATMENT OF INTRACTABLE ASTHMA. ALVAN L. BARACH, J. Allergy **14**:296 (May) 1943.

The article is difficult to abstract because all the known methods of relaxing bronchi were used during the treatment in the 71 cases reported.

Several points of the many brought out in the summary are worth mentioning. Rectal administration of theophylline ethylenediamine produced bronchial relaxation. Combined helium-oxygen and theophylline ethylenediamine therapy produced good results even in intractable asthma the cause of which was not known. In many instances the beneficial effect lasted for more than a year.

HOYER, Cincinnati.

ROENTGEN OBSERVATIONS ON CHILDREN WITH GASTROINTESTINAL ALLERGY TO FOODS. JOSEPH H. FRIES and MARVIN MOGIL, J. Allergy **14**:310 (May) 1943.

Two roentgen studies were made of the gastrointestinal tracts of 30 children ranging in age from 4 to 14 years. In one a 50 per cent suspension of plain barium in water was used; in the other, the allergen in an amount to which the patient had been shown to be sensitive. A week elapsed between the two studies.

"1. Gastric retention was the most common finding. Increased small intestinal segmentation and colonic spasm were also observed, but less frequently.

"2. These effects were due to the allergenicity of food and not to its nutritive composition.

"3. The inclusion of even small amounts of flavoring foodstuffs in barium mixtures may produce alterations in the roentgenograms of allergic individuals."

HOYER, Cincinnati.

SENSITIVITY TO AILANTHUS POLLEN. GEORGE I. BLUMSTEIN, J. Allergy **14**:329 (May) 1943.

Ailanthus glandulosa, tree of heaven, also known as paradise tree, ailanthus, haven-wood and Chinese sumach, is a native of China and was introduced into the United States in 1820. It flowers in June, and pollination lasts for about three weeks.

Two cases of adults sensitive to the pollen are reported. The ocular symptoms were the most pronounced, consisting of severe itching, excessive lacrimation, photophobia and conjunctival injection.

The antigenic activity of pollen obtained from different sources varies greatly.

The author stresses the value of the nasal test in cases of pollen allergy.

HOYER, Cincinnati.

ALLERGY TO FOOD ODORS: ITS RELATION TO THE MANAGEMENT OF INFANTILE ECZEMA. ARTHUR J. HORESCH, J. Allergy **14**:335 (May) 1943.

Nine cases of atopic dermatitis in infants are reported. The allergic symptoms were provoked by the inhalation of vapors or odors from food, either raw or cooked. It seems possible, therefore, that infants may be sensitized to foods by the nasal route, and this factor should be kept in mind in the management of eczema in infants.

HOYER, Cincinnati.

ALLERGENIC RHINITIS DUE TO SPANISH MOSS. GEORGE ADGATE DEAN, J. Allergy **14**:340 (May) 1943.

The author believes that this is the first case reported of sensitivity to Spanish moss. Spanish moss (Tillandsia usneoides) is native to Florida and some other Southern states. It has been used in packing for a long time, and more recently it has been used in upholstery stuffing, since it does not mat with age. It should be thought of as a possible factor in allergic symptoms of the respiratory tract.

HOYER, Cincinnati.

HISTAMINASE IN THE TREATMENT OF ALLERGY IN CHILDREN. M. MURRAY PESHKIN, HOWARD G. RAPAPORT, WILLIAM MESSER, IRVING FEUER, ADELE SICULAR and ARTHUR BERGER, J. Pediat. **22**:426 (April) 1943.

Forty-eight children, ranging in age from 3 to 16 years, who had previously been studied and treated for allergic conditions, were each given 50 units of histaminase (torantil) over a period averaging nine weeks. The allergic manifestations included asthma, hay fever, vasomotor rhinitis, urticaria, migraine and angioneurotic edema. The drug proved to be ineffective not only as a prophylactic agent but as a therapeutic adjunct. In fact, results were poorer than those which one obtains with other nonspecific types of therapy for allergy. The use of histaminase is based on the assumption that his-

tamine is a factor producing smooth muscle spasm and localized edema, manifestations of anaphylaxis and allergy. The authors state that, since this theory has never definitely been proved, the value of a counteracting histaminase is questionable.

STETTENBENZ, Buffalo.

PRINCIPLES OF DIAGNOSIS AND TREATMENT OF ALLERGY AS RELATED TO OTOLARYNGOLOGY. FRENCH K. HANSEL, Laryngoscope **53**:260 (April) 1943.

Allergy is increasing generally. This is because of increasing contact with industrial and automobile dusts, atmospheric molds and pollens, and various chemical substances, drugs and serums.

The diagnosis depends on a complete history and physical examination together with cutaneous tests, cytologic examination of secretions, roentgen study of the sinuses and bacteriologic investigation. Cytologic examination is emphasized.

There are several groups of allergic manifestations. Those most interesting to the otolaryngologists are the perennial nasal and sinal allergy, allergy of the eye and ear, hay fever, allergic bronchitis and bronchial asthma. These are caused mostly by inhalants. Other groups of allergies are given.

It is well to emphasize that the ear may be involved in various ways. There may be eczema and contact dermatitis of the auricle and canal. There may be deafness. This deafness may be a result of swelling of the eustachian tube or of involvement of the eighth nerve (serum sensitivity). Ménière's disease may be the result of allergic sensitivity in some patients.

The salivary glands may also be involved. A painless swelling over the parotid area usually results. It may be bilateral or unilateral. It is caused by a thick mucus plug obstructing Stenson's duct. The saliva contains many eosinophils.

Before removing tonsils and adenoids for the relief of recurring head colds and bronchitis, one should be certain that the colds are not of an allergic nature. One should investigate chronic coughs. These may also be allergic and lead to asthma.

Only rarely does a food allergen cause allergy of the respiratory tract. Cutaneous tests are reliable for pollen sensitivity but often fail to reveal sensitivity to other inhalants (e. g., dust) or to foods.

For allergy due to an inhalant the treatment may be merely avoidance of the allergen. Dust-proof pillow and mattress covers may be employed. Nonallergic cosmetics should be used. There should be no household pets. Sometimes a change of occupation or of residence is necessary. Of the inhalants outside of the pollens, dust is the most common offender.

The author describes a method of preparing extracts of dusts, and other antigens and gives charts showing cutaneous reaction to these antigens. He discusses the strength of solution used and the intervals of administration. He points out that most poor results are due to giving too large initial doses or to increasing the doses too rapidly. In regard to dust allergy the doses should be adjusted to the symptoms rather than to the cutaneous reactions.

Atmospheric pollen counts are important in the evaluation of hay fever. A technic for making these counts and a list of the important pollens are presented. In hay fever, cutaneous reactions are reliable. The scratch or cut method is satisfactory for diagnosis.

When treatment by preseasonal subcutaneous injections is not satisfactory, the intracutaneous method is sometimes beneficial. Coseasonal injections are often highly successful. As with the injections of dust, the initial dose should be small, and the subsequent doses should be regulated according to cutaneous reactions and symptoms. One should remember not to overstep the patient's tolerance. The optimum and not the maximum dose is to be preferred.

HITSCHLER, Philadelphia. [ARCH. OTOLARYNG.]

VITAMIN A ABSORPTION IN INFANTILE ECZEMA. PAUL A. DI SANT'AGNESE and VINCENT DEP. LARKIN, Proc. Soc. Exper. Biol. & Med. **52**:343 (April) 1943.

Four infants with intractable eczema associated with retarded development and malnutrition were given 0.1 cc. of percomorph liver oil (6,000 U. S. P. units of vitamin A per pound [450 Gm.] of body weight), and the blood level of vitamin A was determined immediately and after three, six, nine and ten hours. Definite impairment of absorption of vitamin A was indicated by only slight increases in the vitamin A levels compared with the increases in 4 control subjects.

HANSEN, Minneapolis.

TREATMENT OF SCABIES BY T. E. T. M. S. [TETRAETHYLTHIURAM MONOSULFIDE]. T. M. CLAYTON, Brit. M. J. **1**:443 (April 10) 1943.

The treatment of scabies in rats infested with itch mites with a new preparation, tetraethylthiuram monosulfide, was reported by Gordon and Seaton in 1942. In this article the author reports the use of the same compound for scabies in human beings. The article is well covered in his summary.

"T. E. T. M. S. in 25% emulsion has been found to be curative in 11 out of 14 cases of severe and complicated scabies, the remaining 3 cases being probable reinfections.

"In 15 volunteers and 18 patients the emulsion failed to produce dermatitis or irritation beyond a preliminary smarting in some severe cases.

"In 5% aqueous solution it has proved curative in 93 consecutive cases and produced only mild dermatitis in 7 patients.

"It has proved to be a sacropticide of potency against the human itch-mite and is worthy of extended trial."

BIRDSONG, Charlottesville, Va.

SCABIES IN CHILDREN: DIAGNOSIS, COMPLICATIONS AND TREATMENT. R. T. BRAINS, Practitioner **150**: 231 (April) 1943.

The author discusses the differential diagnosis and the treatment of scabies, alone or in combination with eczema or other dermatitis or with a secondary infection such as impetigo. The article does not readily lend itself to abstracting and should be read in its entirety by those interested. THELANDER, San Francisco.

CASE FOR DIAGNOSIS: EPIDERMOLYSIS BULLOSA HEREDITARIA? THERESE KINDLER, Proc. Roy. Soc. Med. **36**:292 (April) 1943.

The patient, a boy 3 years old, had suffered from a bulbous eruption since fourteen days after his birth. A twin brother had died from a similar disease. Bullae of varied size appeared on normal skin, on any part of the surface. The moist axillary and perianal areas showed papillomatous, condyloma-like excrescences. The mucous membranes, nails and hair were unaffected. The blood was normal except for anemia. Various treatments tried by the author are outlined. None had any effect.

WILLIAMSON, New Orleans.

# Book Reviews

**The Food You Eat, a Practical Guide to Home Nutrition.** By Samuel and Violette Glasstone. Price, $2.25. Pp. 277, with illustrations. Norman, Oklahoma: University of Oklahoma Press, 1943.

According to the publisher's announcement printed on the jacket, this book is intended as "a practical guide for home use" and for "those many agencies which are now engaged in educating consumers toward health for victory." The same announcement states that the book should "prove itself extremely valuable for use by the nutritionist, the dietician and the doctor." After such an introduction it is a surprise to learn that the authors, although competent in other fields of science, are not persons with special training in nutrition, and it is a shock to find the many inaccuracies, misstatements and incorrect interpretations of scientific facts which the book contains. Although the information concerning the chemistry of food is in the main correct, much of the other material included in the text apparently has been derived from scientifically unreliable sources. The book is attractively illustrated and well indexed but contains no bibliography.

Perhaps the most amazing feature of this book is the apparently serious description of a (to say the least) novel "nonoperative" procedure for the cure of skeletal deformities due to rickets. In essence, this procedure consists of the production of rickets severe enough to soften the bones "to the point where they may be bent naturally to the desired position." The limb is then straightened and placed in a cast of plaster of paris. Finally, the rickets is cured and the bone hardened in its new position by changing the diet to include foods rich in calcium, phosphorus and vitamin D. What may happen to other bony structures, such as the pelvis and the skull, while the patient is undergoing this unique treatment is not mentioned.

Although quantitative statements are made concerning individual requirements for each of the various dietary essentials, no reference is made to the now widely accepted "recommended dietary allowances" of the Committee on Food and Nutrition of the National Research Council. The quantities of the various nutrients recommended by these authors do not conform to currently accepted standards. Other dietary recommendations which are not in accord with the modern knowledge of nutrition are the advice to reduce the protein content of the diet with "increasing age"; to avoid sweetened drinks, such as ice cream soda, in hot weather, because "sugar and starch are fuel foods which increase the temperature of the body," and to avoid the use of two or more foodstuffs rich in carbohydrate at any one meal "unless the portions of each are small." The advice given concerning the use of vitamin concentrates is contrary to that given by authorities in nutrition, as is the statement that since very few people are in a position to eat a leisurely breakfast, a light breakfast or no breakfast at all is advisable!

Other scientific inaccuracies to be found in this book are too numerous to be included in a short review. It is a pity that when good popular books on nutrition are as much in demand as they are today this one cannot be recommended. On the contrary, this book can only be said to serve as an unfortunate example of what may happen when persons competent in one field of science attempt to speak authoritatively in other fields, however closely related they may seem to be.

**Urology in General Practice.** By Nelse F. Ockerblad, M.D., and Hjalmar E. Carlson, M.D. Price, $4.00. Pp. 383, with 98 illustrations. Chicago: The Year Book Publishers, Inc., 1943.

From the title is to be assumed that this book is written for the general practitioner, but as such it falls short of the objective.

In the opening chapter on urologic diagnosis some of the important tests of renal function, such as studies of chemical constituents in the blood (nonprotein nitrogen, urea nitrogen, uric acid and creatinine), urea clearance tests, the Mosenthal test and the Neuburgh test, are not even mentioned. Many pages are written to teach the general practitioner how to do highly specialized urologic procedures, such as cystoscopy and ureteral catheterization. It would seem that what the eye sees and interprets through the cystoscope is far more important than the manipulation of the instrument.

In the discussion of the causes of hematuria from the bladder the authors stress only papilloma and do not mention cancer. Not every urologist will agree with their statement that all papillomas are malignant. In view of the fact that malignant tumors of the kidney are prone to produce metastases in the bones and in the lungs, it would seem important to emphasize to the general practitioner the need for roentgen studies of the bones and the lungs before use of nephrectomy is contemplated.

In the treatment of the Wilms tumor no mention is made of the preoperative use of roentgen therapy, a procedure which has resulted in great reduction of operative mortality.

In the treatment of cancer of the prostate gland castration and the use of diethyl stilbestrol are presented in detail. One is impressed by the authors' statement that in their series of 18 cases of cancer of the prostate gland they had practically 100 per cent good results.

The chapter on diseases of the external genitals of the male is well done.

The chapter on sterility and impotence is an excellent presentation of these subjects.

The use of the sulfonamide compounds is given in detail, as is the present day treatment of gonorrheal vaginitis.

The book contains 93 illustrations. One is impressed by the fact that so many of the pyelograms have been made by the retrograde and not by the intravenous route. Details of operative technic are lacking.

With so many standard textbooks available to the general practitioner one wonders why this book was written.

**Nicholas Copernicus, 1543-1943.** By Stephen P. Mizwa, A.M., LL.D. Price, not given. Pp. 88, with 20 illustrations. New York: The Kosciuszko Foundation, 1943.

This is a short sketch of the life of Nicholas Copernicus and his works; it contains a chapter on his genealogy in order to prove his Polish ancestry. This book is issued by the Kosciuszko Foundation in an effort to set before the American people the claims of Polish culture. It is profusely and well illustrated and is altogether an acceptable contribution to medical history, since Copernicus happens to have been a physician.

# Directory of Pediatric Societies *

## INTERNATIONAL

### International Association of Preventive Pediatrics

President: Prof. S. Monrad, Dronning Louises Børnehospital, Copenhagen, Denmark.
Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.

### International Congress of Pediatrics

President: Dr. Henry F. Helmholz, Mayo Clinic, Rochester, Minn.
Secretary-Treasurer: Dr. Charles F. McKhann, University Hospital, Ann Arbor, Mich.
Canadian Committee:
Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto.
Secretary: Dr. H. P. Wright, 1509 Sherbrooke St. W., Montreal.
Place: Boston. Time: Postponed indefinitely.

### International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

## FOREIGN

### Argentine Pediatric Society of Buenos Aires

President: Dr. Martin Ramón Arana, 1809 Rodriguez Peña, Buenos Aires.
General Secretary: Dr. Alfredo Larguia, Cerrito 1179, Buenos Aires.

### Associação Paulista de Medicina, Section on Pediatrics

President: Dr. Vicente Lara.
First Secretary: Dr. Armando de Arruda Sampaio.
Second Secretary: Dr. Paulo de Barros Franca, Av. Brigadeiro Luiz Antonio 393, 1° Andar, São Paulo, Brazil.

### British Paediatric Association

President: Prof. L. G. Parsons, 58 Calthorpe Rd., Five Ways, Birmingham.
Secretary: Dr. Donald Paterson, 27 Devonshire Pl., London, W. 1.

### Danish Pediatric Society

President: Dr. E. Lenstrup, Copenhagen.
Secretary: Dr. E. Gjørup, Dronning Louises Børnehospital, Copenhagen.

### Nederlandische Vereeniging voor Kindergeneeskunde

President: Dr. J. H. G. Carstens, Servaasbolwerk 14ª, Utrecht.
Secretary: Dr. R. P. van de Kasteele, Laan van Poot 340,'s Gravenhage.
Place: Different places. Time: Three times a year.

### Paediatrický Spolok na Slovensku

President: Dr. A. J. C. Chura, Lazaretská 11, Bratislava.
Secretary: Dr. P. Rados, Lazaretská 6, Bratislava.
Place: Pediatric Clinic, University Bratislava. Time: Six times a year.

### Royal Society of Medicine, Section for the Study of Disease in Children

President: Dr. E. A. Cockayne, 98 Harley St., London, W. 1, England.
Secretary: Dr. R. Lightwood, 86 Brook St., London, W. 1, England.
Place: 1 Wimpole St., London. Time: Fourth Friday of each month, 4:15 p. m.

### Palestine Jewish Medical Association, Section of Physicians of Children's Diseases

President: Prof. S. Rosenbaum, 26 Bialkstr., Tel Aviv.
Secretary: Dr. A. Brünn, 9 Maazestre, Tel Aviv.

### Sociedad Cubana de Pediatria

President: Dr. Angel A. Aballí Arellano, 17 No. 609 Vedado, Habana.
Secretary: Dr. Julio G. Cabrera Calderin, Hospital Mercedes L y 21 (Vedado), Box 2430, Habana.
Place: Cátedra de Clinica Infantil, Hospital Mercedes, Habana. Time: Last Wednesday of every month.

### Sociedad Mexicana de Pediatria

President: Dr. Fernando López Clares, 12/a. Medellín 191, Mexico.
Secretary: Dr. Jesus Gómez Pagola, Versalles 64, Mexico.

### Sociedad Venezolana de Puericultura y Pediatria

President: Dr. E. Santos Mendoza.
Secretary: Dr. P. Oropeza, Hospital de Niños, Caracas.

### Société de Pédiatrie de Paris

President: Dr. B. Weill-Hallé, 49 Avenue Raymond Poincare, Paris, France.
Secretary: Dr. Jean Hallé, 10 bis Rue Pré aux Clercs, Paris, France.
Place: Hôpital des Enfants Malades, 49 Rue de Sèvres. Time: 4:30 p. m., third Thursday of every month.

### Uruguyan Society of Pediatrics

President: Dr. Jose Alberto Praderi, Eduardo Acevedo 1132, Montevideo.
Secretary: Dr. Alfredo Ramon Guerra, Paysandú 824, Montevideo.

## NATIONAL

### American Medical Association, Scientific Assembly, Section on Pediatrics

Chairman: Dr. Hugh L. Dwyer, 315 Alameda Rd., Kansas City, Mo.
Secretary: Dr. Gilbert J. Levy, 188 S. Bellevue Blvd., Memphis, Tenn.
Place: Chicago. Time: June 12-16, 1944.

### American Academy of Pediatrics

President: Dr. Franklin P. Gengenbach, 1850 Gilpin St., Denver, Colo.
Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

### American Hospital Association, Children's Hospital Section

Chairman: Dr. Joelle C. Hiebert, 299 Main St., Lewiston, Maine.
Secretary: Dr. W. Franklin Wood, McLean Hospital, Waverly, Mass.

### American Pediatric Society

President: Dr. James L. Gamble, 300 Longwood Ave., Boston.
Secretary-Treasurer: Dr. Hugh McCulloch, 325 N. Euclid Ave., St. Louis.

### Canadian Society for the Study of Diseases of Children

President: Dr. R. R. Struthers, 906 Drummond Medical Bldg., Montreal.
Secretary-Treasurer: Dr. Elizabeth Chant Robertson, Hospital for Sick Children, Toronto.

### Society for Pediatric Research

President: Dr. Joseph A. Johnston, Henry Ford Hospital, Detroit.
Secretary: Dr. Mitchell I. Rubin, 1740 Bainbridge St., Philadelphia.

## SECTIONAL

### Intermountain Pediatric Society

President: Dr. Eugene Smith, 385–24th St., Ogden, Utah.
Secretary-Treasurer: Dr. W. C. Cheney, 837 Boston Bldg., Salt Lake City.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

### New England Pediatric Society

President: Dr. Warren R. Sisson, 319 Longwood Ave., Boston.
Secretary-Treasurer: Dr. James Marvin Baty, 1101 Beacon St., Brookline, Mass.
Place: Boston Medical Library. Time: Four meetings a year, occurring from September to May.

### North Pacific Pediatric Society

President: Dr. M. L. Bridgeman, 1020 S. W. Taylor St., Portland, Ore.
Secretary: Dr. C. G. Ashley, 833 S. W. 11th Ave., Portland, Ore.

### Northwestern Pediatric Society

President: Dr. Arild E. Hansen, University of Minnesota, Minneapolis.
Secretary-Treasurer: Dr. Albert V. Stoesser, 205 W. University Hospital, Minneapolis.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

### Rocky Mountain Pediatric Society

President: Dr. G. R. Fisher, 23 E. Pikes Peak Ave., Colorado Springs, Colo.
Secretary: Dr. Joseph H. Lyday, 1850 Gilpin St., Denver.

### Southern Medical Association, Section of Pediatrics

Chairman: Dr. William Weston Jr., 1428 Lady St., Columbia, S. C.
Secretary. Dr. Angus McBryde, 604 W. Chapel Hill St., Durham, N. C.

## STATE

### Alabama Pediatric Society

President: Dr. Amas Gipson, 948 Forrest Ave., Gadsen.
Secretary-Treasurer: Dr. Ruth Berrey, 2021–6th Ave. N., Birmingham.

### Arizona Pediatric Society

President: Dr. Vivian Tappan, San Clemente, Tucson.
Secretary: Dr. Hilda Kroeger, Arizona State Health Dept. (Maternal and Child Welfare Division), Phoenix.

### Arkansas State Pediatric Association

Chairman: Dr. C. B. Billingsley, 1425 N. 11th St., Fort Smith.
Secretary: Dr. R. E. Weddington, 1425 N. 11th St., Fort Smith.

### California State Medical Society, Section on Pediatrics

Chairman: Dr. William C. Deamer, University of California Hospital, San Francisco.
Secretary: Dr. Charles W. Leach, 2000 Van Ness Ave., San Francisco.

### Florida State Pediatric Society

President: Dr. Ludo Von Meysenbug, Box 3356, Daytona Beach.
Secretary: Dr. Robert Blessing, 409 Blount Bldg., Ft. Lauderdale.
Place: Concurrent with state association meeting at time of convention.

### Georgia Pediatric Society

President: Dr. T. F. Davenport, 104 Ponce de Leon Ave. N. E., Atlanta.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.

### Hezekiah Beardsley Pediatric Club of Connecticut

President: Dr. Edward T. Wakeman, 129 Whitney Ave., New Haven.
Secretary: Dr. Herman Yannet, Southbury Training School, Southbury.
Time: Three meetings a year.

### Illinois State Medical Society, Section on Pediatrics

Chairman: Dr. Craig D. Butler, 715 Lake St., Oak Park.
Secretary: Dr. A. J. Fletcher, 139 N. Vermilion, Danville.

### Indiana State Pediatric Society

President: Dr. K. T. Knode, 1105 E. Jefferson Bldg., South Bend.
Secretary-Treasurer: Dr. Mathew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

### Iowa Pediatric Society

President: Dr. Mark L. Floyd, Children's Hospital, Iowa City.
Secretary-Treasurer: Dr. James Dunn, Davenport Bank Bldg., Davenport.

MEDICAL SOCIETY OF STATE OF NEW YORK, SECTION ON PEDIATRICS

Chairman: Dr. A. Clement Silverman, 608 E. Genesee St., Syracuse.
Secretary: Dr. Albert G. Davis, 307 Gas and Electric Bldg., Utica.

MEDICAL SOCIETY OF THE STATE OF PENNSYLVANIA, PEDIATRIC SECTION

Chairman: Dr. Elwood W. Stitzel, 403 Central Trust Bldg., Altoona, Pa.
Secretary: Dr. P. F. Lucchesi, Philadelphia Hospital, Philadelphia.

MICHIGAN STATE MEDICAL SOCIETY, PEDIATRIC SECTION

Chairman: Dr. Charles F. McKhann, University Hospital, Ann Arbor.
Secretary: Dr. Mark F. Osterlin, Central Michigan Children's Clinic, Traverse City.

MISSISSIPPI STATE PEDIATRIC SOCIETY

President: Dr. Harvey F. Garrison Jr., 315 E. Capitol Pl., Jackson.
Secretary: Dr. Guy Verner, 126 N. Congress St., Jackson.

NEBRASKA PEDIATRIC SOCIETY

President: Dr. E. W. Hancock, 820 Sharp Bldg., Lincoln.
Secretary-Treasurer: Dr. John M. Thomas, 1102 Medical Arts Bldg., Omaha.
Place: As announced by committee. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

NEW HAMPSHIRE PEDIATRIC SOCIETY

President: Dr. MacLean J. Gill, 14 N. State St., Concord.
Secretary-Treasurer: Dr. Ursula G. Sanders, 46 Pleasant St., Concord.
Time: Twice yearly.

NORTH CAROLINA PEDIATRIC SOCIETY

President: Dr. Arthur H. London, 1105 W. Main St., Durham.
Secretary: Dr. Jay M. Arena, 604 W. Chapel Hill St., Durham.

OKLAHOMA STATE PEDIATRIC SOCIETY

President: Dr. Ben H. Nicholson, 301 N. W. 12th St., Oklahoma City.
Secretary: Dr. Luvern Hays, 108 W. 6th St., Tulsa.
Place: Oklahoma Club. Time: 6:30 p. m., fourth Friday of each alternate month from September to May, inclusive.

SOUTH CAROLINA PEDIATRIC SOCIETY

President: Dr. Lonita Boggs, 301 E. Coffee St., Greenville.
Secretary-Treasurer: Dr. Hilla Sheriff, Wade Hampton Office Bldg., Columbia.

TEXAS PEDIATRIC SOCIETY

President: Dr. F. H. Lancaster, 4409 Fannin St., Houston.
Secretary-Treasurer: Dr. John E. Ashby, 3610 Fairmount Ave., Dallas.

VIRGINIA PEDIATRIC SOCIETY

President: Dr. Edwin A. Harper, 301 Rivermont Ave., Lynchburg.
Secretary: Dr. Emily Gardner, 1100 W. Franklin St., Richmond.

WEST VIRGINIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

President: Dr. Andrew Amick, 1021 Quarrier St., Charleston.
Secretary: Dr. A. A. Shawkey, Professional Bldg., Charleston.

## LOCAL

ACADEMY OF MEDICINE OF CLEVELAND PEDIATRIC SECTION

Chairman: Dr. J. D. Nourse, 10515 Carnegie Ave., Cleveland.
Secretary: Dr. I. B. Silber, 10465 Carnegie Ave., Cleveland.
Place: Cleveland Medical Library Bldg. Time: October, December, February and April.

ACADEMY OF MEDICINE, TORONTO, SECTION OF PEDIATRICS

President: Dr. I. Nelles Silverthorne, 170 St. George St., Toronto, Canada.
Secretary: Dr. G. P. Hamblin, 2333 Bloor St. W., Toronto, Canada.

BRONX PEDIATRIC SOCIETY

President: Dr. Harry J. Cohen, 1975 Walton Ave., New York.
Secretary: Dr. Walter Levy, 12 E. 88th St., New York.
Place: Concourse Plaza Hotel, 161st St., and Grand Concourse. Time: Second Wednesday of each month, except June, July, August and September.

BROOKLYN ACADEMY OF PEDIATRICS

President: Dr. Harry A. Naumer, 37–8th Ave., Brooklyn.
Secretary: Dr. Lewis A. Koch, 62 Pierrepont St., Brooklyn.
Place: Granada Hotel. Time: Fourth Wednesday of October, November, February, March and April.

BUFFALO PEDIATRIC SOCIETY

President: Dr. A. Wilmot Jacobsen, 187 Bryant St., Buffalo N. Y.
Secretary: Dr. Richard A. Downey, 786 Forest Ave., Buffalo, N. Y.
Place: Children's Hospital, 219 Bryant St. Time: 8:30 p. m., first Monday of each month from September to June.

CENTRAL NEW YORK PEDIATRIC CLUB

President: Dr. Edward J. Wynkoop, 501 James St., Syracuse.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Places:: Various cities in New York. Time: Third Tuesday of April and September.

CHICAGO PEDIATRIC SOCIETY

President: Dr. Heyworth N. Sanford, 952 N. Michigan Ave., Chicago.
Secretary: Dr. Henry G. Poncher, 1819 W. Polk St., Chicago.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May, Inclusive.

### Cincinnati Pediatric Society

President: Dr. Lloyd K. Felter, 3144 Jefferson Ave., Cincinnati.
Secretary: Dr. T. Selkirk, 3530 Reading Rd., Cincinnati.
Place: Children's Hospital, Elland Ave., Cincinnati. Time: On call.

### Dallas Pediatric Society

President: Dr. John E. Ashby, 3610 Fairmount Ave., Dallas, Texas.
Secretary-Treasurer: Dr. Gladys J. Fashena, 4585 Belfort, Dallas, Texas.
Place: Bradford Baby Hospital. Time: 1 p. m., second and fourth Saturdays of each month.

### Detroit Pediatric Society

President: Dr. Hugh Lewis, Detroit, Mich.
Secretary: Dr. John J. Pollack, 622-26 Maccabees Bldg., Detroit, Mich.
Place: Wayne County Medical Society. Time: 8:30 p. m., first Wednesday of each month from October to June, inclusive.

### Fulton County Medical Society, Pediatrics Section (Atlanta, Ga.)

Chairman: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.
Secretary: Dr. Harry Lange, 478 Peachtree St., N. E., Atlanta.
Place: Academy of Medicine, 38 Prescott St. N. E. Time: Second Thursday of each month from October to April, 8 p. m.

### Houston Pediatric Society

President: Dr. Raymond Cohen, 2300 Caroline St., Houston, Texas.
Secretary: Dr. Betty Moody, 526 Richmond Rd., Houston, Texas.
Place: College Inn, Houston. Time: Fourth Monday of each month.

### Kansas City (Missouri) Pediatric Society

President: Dr. Edwin H. Schorer, 1103 Grand Ave., Kansas City.
Secretary: Dr. H. E. Petersen, Kirkpatrick Bldg., St. Joseph, Mo.
Place: Kansas City General Hospital. Time: On call.

### Los Angeles County Medical Association, Pediatric Section

President: Dr. Oscar Reiss, 2200 W. 3d St., Los Angeles.
Secretary-Treasurer: Dr. Elena Boder, 1830½ Lucille Ave., Los Angeles.
Place: Los Angeles County Medical Headquarters, 1925 Wilshire Blvd. Time: Second Monday of February, April, June, October and December.

### Medical Society of the County of Kings and the Academy of Medicine of Brooklyn, Pediatric Section

President: Dr. Harry Bikoff, 850 St. Marks Ave., Brooklyn.
Secretary: Dr. Henry Rascoff, 895 Eastern Parkway, Brooklyn.
Place: 1313 Bedford Ave., Brooklyn. Time: 9:00 p. m., fourth Monday of each month, October to April, inclusive.

### Medical Society of the County of Queens, Inc., Section on Pediatrics

Chairman: Dr. Meyeron Coe, 217-02-91st Ave., Queens Village, N. Y.
Secretary-Treasurer: Dr. Edith A. Mittell, 144-38th Ave., Flushing, N. Y.
Place: Queens County Medical Bldg., Forest Hills, N. Y. Time: Third Monday of October, January, March and May.

### Medical Society of the District of Columbia, Section on Pediatrics

President: Dr. Harry A. Spigel, 2647 Connecticut Ave., Washington, D. C.
Secretary-Treasurer: Dr. Perry W. Gard, 2520 Woodley Rd., Washington, D. C.
Place: Medical Society Bldg., 1718 M St. N. W. Time: 8 p. m., fourth Thursday of every month.

### Memphis Pediatric Society

President: Dr. F. T. Mitchell, 376 S. Bellevue Ave., Memphis, Tenn.
Secretary-Treasurer: Dr. Harry Jacobson, 1193 Madison Ave., Memphis, Tenn.
Place: John Gaston Hospital. Time: Quarterly.

### Milwaukee Pediatric Society

President: Dr. John H. Reynolds, 1628 W. Wisconsin Ave., Milwaukee.
Secretary-Treasurer: Dr. F. J. Mellencamp, 324 E. Wisconsin Ave., Milwaukee.
Place: Milwaukee Athletic Club. Time: Second Wednesday of each alternate month, beginning with February.

### New York Academy of Medicine, Section of Pediatrics

Chairman: Dr. Edith M. Lincoln, 600 Park Ave., New York.
Secretary: Dr. Alfred E. Fischer, 73 E. 90th St., New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from October to May, inclusive, 8:30 p. m.

### Northern California Affiliates

President: Dr. Crawford Bost, 490 Post St., San Francisco.
Secretary: Dr. William A. Reilly, 384 Post St., San Francisco.
Time: Second Thursday of September, November, January, March and May.

### Oklahoma City Pediatric Society

President: Dr. William M. Taylor, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. G. R. Felts, 625 N. W. 10th St., Oklahoma City.
Place: Oklahoma Club. Time: Third Thursday of each month.

### Philadelphia Pediatric Society

President: Dr. Theodore S. Wilder, Greene and Coulter Sts., Germantown, Philadelphia.
Secretary: Dr. Sherman Little, 1740 Bainbridge St., Philadelphia.
Place: College of Physicians, 19 S. 22d St. Time: Second Tuesday in March, May, October and December.

### Pittsburgh Pediatric Society

President: Dr. Carl Ruder, 646 Washington Rd., Mount Lebanon, Pittsburgh.

Secretary-Treasurer: Dr. C. J. Stoecklein, 125 De Soto St., Pittsburgh.

Place: Pittsburgh Academy of Medicine. Time: Second Friday, alternate month from October to June, inclusive.

### Richmond Pediatric Society

President: Dr. Stanley Meade, 913 Floyd Ave., Richmond, Va.

Secretary-Treasurer: Dr. Louise Galvin, 214 S. Boulevard, Richmond, Va.

Place: Richmond Academy of Medicine, 1200 E. Clay St. Time: 8 p. m., third Thursday of each month, except June, July and August.

### Rochester Pediatric Society

President: Dr. Herbert Soule, 122 Rutgers St., Rochester, N. Y.

Secretary-Treasurer: Dr. Jerome Glaser, 300 S. Goodman St., Rochester, N. Y.

Place: Rochester Academy of Medicine or arrangement by program committee. Time: Third Friday of each month from October to May.

### St. Louis Pediatric Society

President: Dr. Jerome Diamond, 508 N. Grand Ave., St. Louis.

Secretary-Treasurer: Dr. Mary A. McLoon, 408 Humboldt Bldg., St. Louis.

Place: St. Louis Medical Society Bldg. Time: First Friday of each month from November to June.

### Seattle Pediatric Society

President: Dr. Frederick B. Joy, Stimson Bldg., Seattle.

Secretary: Dr. Sherod M. Billington, Medical Dental Bldg., Seattle.

Place: College Club. Time: Third Friday of each month from September to June at 6:30 p. m.

### Southwestern Pediatric Society

President: Dr. Jeanette Harrison, 1136 W. 6th St., Los Angeles.

Secretary: Dr. Henry F. Gallagher, 1930 Wilshire Blvd., Los Angeles.

Place: Jonathan Club of Los Angeles. Time: First Wednesday in January, March, May, September and November.

### University of Michigan Pediatric and Infectious Disease Society

President: Dr. Campbell Harvey, 35 W. Huron St., Pontiac, Mich.

Secretary: Dr. Harry A. Towsley, University of Michigan, Department of Pediatrics and Communicable Diseases, Ann Arbor, Mich.

### Westchester County Medical Society, Pediatrics Section (New York)

President: Dr. John B. Ahouse, 27 Ludlow St., Yonkers, N. Y.

Secretary-Treasurer: Dr. Elvira Ostlund, 64 Highland Rd., Rye, N. Y.

Place: Grasslands Hospital, Valhalla, N. Y. Time: Third Thursday in October, December, February and April.